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DECLARATION

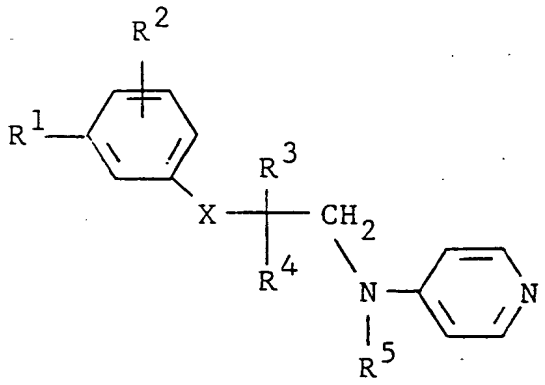
I, Dr. Manfred WEBER, Roche Diagnostics GmbH of
Sandhofer Straße 116, 68298 Mannheim, Federal Republic of Germany,
declare that I have a competent knowledge of the English and German languages
and that the attached document ist a true and accurate translation of the text of
European Patent Specification No. 0 687 253 from German into English.

Dated this 29th day of January 1999

M. Weber

Dr. Weber

The invention concerns new 4-aminopyridines of the general formula I



(I),

in which

R^1 denotes the group R^6-SO-NR^7, R^6-SO_2-NR^7, R^6-NR^7-SO-, R^6-NR^7-SO_2-, R^6-SO-O-, R^6-SO_2-O-, R^6-O-SO- or R^6-O-SO_2-,

R^2 denotes a hydrogen or halogen atom, a cyano, C_1-C_4-alkyl, C_1-C_6-alkoxy or halo-C_1-C_6-alkyl group,

X denotes an oxygen atom, a sulphur atom or the NH group,

R^3 and R^4 are the same or different and denote hydrogen atoms or C_1-C_6-alkyl groups,

R^5 denotes a hydrogen atom, a C_1-C_6-alkyl group or the aralkyl group,

R^6 denotes a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, aryl, aralkyl or a mono-, bi- or tricyclic aromatic system with heteroatoms, such as nitrogen, oxygen and sulphur, which can be linked with a C_1-C_6-alkyl group which, like the aryl radical, can be substituted one or several times by nitro, halogen, nitrile, hydroxy, amino, carboxy, C_1-C_6-alkoxy-carbonyl, C_2-C_6-alkenyloxycarbonyl, C_2-C_6-alkynyloxycarbonyl, aralkoxycarbonyl, C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl,

cyano-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyloxy, C_2-C_6-alkynyloxy, aralkyloxy, cyano-C_1-C_6-alkyloxy, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, aralkylamino, di-aralkylamino, C_1-C_6-alkylsulfonylamino, C_1-C_6-alkylcarbonylamino, formylamino, aminocarbonyl, C_1-C_6-alkylaminocarbonyl, di-C_1-C_6-alkylaminocarbonyl or by one or more of the groups -Y-CO_2R^8, -S-Y-CO_2R^8, -O-Y-CO_2r^8, -NH-Y-CO_2R^8, -S-Y-$CONR^8R^9$, -O-Y-CO-NR^8R^9 or -NH-Y-$CONR^8R^9$, whereby the alkyl, alkenyl or alkynyl fragments can be substituted one or several times by halogen, hydroxy, C_1-C_6-alkoxy, C_1-C_6-alkylcarbonyloxy, amino or carboxy groups,

R^7 denotes a hydrogen atom, a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl residue, whereby these residues can be substituted one or more times by halogen, hydroxy, C_1-C_6-alkoxy, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, carboxy, C_1-C_6-alkylcarbonyl or C_1-C_6-alkoxycarbonyl, or denote the C_1-C_6-alkoxycarbonyl, cyano-C_1-C_6-alkyl, aryl, aralkyl or a mono-, bi- or tricyclic aromatic system with heteroatoms, such as nitrogen, oxygen and sulphur, which can be linked with a C_1-C_6-alkyl group which, like the aryl radical, can be substituted one or more times by halogen, nitrile, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyloxy, C_2-C_6-alkynyloxy, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, halo-C_1-C_6-alkoxy, hydroxy, carboxy, hydroxy-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, C_1-C_6-alkylsulfonylamino, C_1-C_6-alkylcarbonylamino, formylamino, aminocarbonyl or phenyl, or denotes a -Y-CO_2R^8 or -Y-$CONR^8R^9$ group.

Y denotes a linear or branched alkylene chain,

R^8 and R^9 are the same or different and denote hydrogen atoms, aralkyl, C_3-C_7-cycloalkyl or C_1-C_6-alkyl groups, which can be substituted one or more times by halogen, hydroxy, C_1-C_6-alkoxy, C_1-C_6-alkyl-carbonyloxy, amino or carboxy, or R^8 and R^9, together with the N-atom to which they are bound, form a saturated ring which can contain an additional oxygen, sulphur or nitrogen atom,

as well as hydrates, solvates and physiologically compatible salts thereof. The subject of the invention are also the optically-active forms, the racemates and the diastereomeric mixtures of these compounds.

The invention also concerns processes for the production of the above compounds, medicaments which contain such compounds as well as the use of these compounds in the production of medicaments.

The aminopyridines of the general formula I, their solvates and their salts inhibit not only the coagulation of fibrinogen in blood induced by thrombin but also the aggregation of blood platelets induced by thrombin. Thus, they prevent formation of coagulation thrombi and of platelet-rich thrombi and can be used in the combatting and prevention of diseases such as thrombosis, apoplexy, heart infarction, inflammations and arteriosclerosis. Furthermore, these compounds have an effect on tumour cells and prevent formation of metastases. Thus, they can be used as anti-tumour agents.

Thrombin, the last enzyme of the coagulation cascade, cleaves fibrinogen to fibrin which is cross-linked by factor XIIIa and becomes an insoluble gel which forms the matrix for a thrombus. Thrombin activates the platelet aggregation by proteolysis of its receptor on the blood platelets and, in this way,

also contributes to the thrombus formation. In the case of damaging of a blood vessel, these processes are necessary in order to stop a bleeding. No measurable thrombin concentrations are present in blood plasma under normal circumstances. Increases of the thrombin concentration can lead to the formation of thrombi and hence to thromboembolic diseases which occur very frequently above all in industrial countries.

Thrombin is kept ready in the plasma in the form of prothrombin and is released from this by factor Xa. Thrombin activates factors V, VIII and XI whereby the factor X is converted into Xa. Thrombin thereby catalyses its own release which is why very rapidly increasing in thrombin concentrations can occur.

Thrombin inhibitors can, therefore, inhibit the release of thrombin, the platelet-induced and the plasmatic blood coagulation.

Apart from thrombin, there exist a whole series of serine proteases which cleave peptide substrates next to a basic amino acid. In order to limit side-effects, the thrombin inhibitors should be selective i.e. they should inhibit other serine proteases only slightly or not at all. Especially trypsin as most nonspecific serine protease, can be easily inhibited by the most varied inhibitors. Trypsin inhibition can lead to pancreatic stimulation and to pancreatic hypertrophy (J.D. Geratz, Am. J. Physiol. 216, (1969), p. 812).

Plasma contains the protein plasminogen which is converted into plasmin by activators. Plasmin is a proteolytic enzyme the activity of which resembles that of trypsin. It serves to dissolve thrombi in that it breaks down fibrin. Inhibition of plasmin would thus have the opposite effect to that which one would like to achieve by the inhibition of the thrombin.

Synthetic thrombin inhibitors have already been known for a long time. Starting from fibrinogen, the natural substrate of thrombin, substances of the (D)-Phe-Pro-Arg type have been synthesised. Such tripeptides imitate the amino acid sequence before the cleavage site on fibrinogen. In order to obtain good inhibitors, the carboxylate group of the arginine was thereby so changed that the hydroxy group of serine 195 in the active site of thrombin can react with it. This is, for example, possible in that one replaces the carboxylate group by the aldehyde function. Corresponding (D)-Phe-Pro-arginals are described in the Patent Application EP-A 185390.

Benzamidine, a known trypsin inhibitor, was taken as the basis for a second type of thrombin inhibitor. The so-obtained inhibitors differ from the (D)-Phe-Pro-Arg types not only in the chemical structure but also in the manner of the inhibition: serine 195 of thrombin does not bind to these inhibitors. This clearly follows from X-ray structure examinations (W. Bode, D. Turk, J. Sturzebecher, Eur. J. Biochem. 193, 175-182 (1990)). Nα-(2-naphthylsulfonylglycyl)-4-amidino-(R,S)-phenylalanine-piperidide ("NAPAP", DD 235866) belongs to this second class of thrombin inhibitors.

Surprisingly, it has now been found that compounds of the general formula I, which show no common structural features with known thrombin inhibitors, are selective thrombin inhibitors.

The alkyl or alkoxy fragments mentioned in the definitions of R^1 - R^9 contain 1-6 carbon atoms, whereby these fragments can be straight-chained or branched. The same applies to the corresponding alkenyl or alkynyl fragments. Cycloalkyl groups are rings with three to seven carbon atoms. In the case of a haloalkyl or haloalkoxy group, the alkyl or alkoxy

group can be substituted once, twice or three times by halogen. The trifluoromethyl or trifluoromethoxy group preferably comes into consideration in the case of groups substituted three times by halogen. In all cases, halogen denotes fluorine, chlorine, bromine or iodine. By aralkyl and aralkoxy groups, one preferably understands the benzyl or benzyloxy group. In those cases in which the said groups can be substituted one or more times, a single, double or triple substitution comes into particular consideration. In the case of the six-membered rings, in the aryl or heteroaryl groups, the substituents can, independently of one another, be in the ortho, meta or para position.

If one of the substituents R^2 - R^9 in the general formula I denotes an alkyl group or R^6 denotes an aryl or heteroaryl group substituted by one or more alkyl groups, then, under the alkyl groups, are to be understood straight-chained or branched alkyl groups with 1 to 6 carbon atoms, preferably the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, pentyl and the hexyl group. Under the halogen atoms as substituents on the alkyl groups are understood fluorine, chlorine, bromine or iodine, preferably fluorine and chlorine. The trifluoromethyl, chloromethyl, 2-chloroethyl and the 3-chloropropyl group are preferred. If the alkyl groups are substituted by hydroxy groups, then the hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, 1,2-dihydroxyethyl and the 2,3-dihydroxypropyl group are preferred. If the alkyl groups are substituted by alkoxy groups, then the methoxymethyl, ethoxymethyl, methoxyethyl and ethoxyethyl group are preferred. If the alkyl groups are substituted by amino groups, then the aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl and the 5-aminopentyl group are preferred. If the alkyl groups

are substituted by carboxy groups, then the carboxymethyl, 1-carboxyethyl, 2-carboxyethyl and 2-methyl-1-carboxyethyl group are particularly preferred.

If R^6, R^7, R^8 or R^9 in the general formula I denote a cycloalkyl group or if R^6 denotes an aryl or heteroaryl group substituted with a cycloalkyl group, then under the cycloalkyl groups are to be understood rings with 3 to 7 members, preferably the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the cycloheptyl group. In all cases, the cycloalkyl group can also be linked via an alkyl group so that a cycloalkyl-alkyl group results as substituent. The cyclopropylmethyl and the cyclohexylmethyl group are thereby particularly preferred.

If R^6 in the general formula I denotes an aryl or heteroaryl group substituted with an alkenyl residue or if R^7 denotes an alkenyl residue, then straight-chained or branched residues with 3 to 6 members, preferably the allyl, butenyl and isobutenyl residue, are to be understood thereunder.

If R^6 in the general formula I denotes an aryl or heteroaryl group substituted with an alkynyl residue or if R^7 denotes an alkynyl residue, then straight-chained or branched residues with 3 to 6 members, preferably the propargyl residue, are to be understood thereunder.

If R^6 in the general formula I denotes an aryl or heteroaryl group substituted with an alkoxycarbonyl, alkenyloxycarbonyl or alkynyloxycarbonyl residue, then straight-chained or branched residues with 2 to 6 carbon atoms, preferably the methoxycarbonyl, ethoxycarbonyl and allyloxycarbonyl group, are to be understood thereunder.

If R^6 in the general formula I denotes an aryl or heteroaryl group substituted with an alkoxy residue, then straight-chained or branched residues with 1 to 6

carbon atoms are to be understood thereunder, preferably the methoxy, ethoxy, propyloxy, butyloxy and the pentyloxy group. If the alkoxy groups are substituted by hydroxy groups, then the 2-hydroxyethoxy, 3-hydroxypropyloxy and the 2,3-dihydroxypropyloxy group are preferred. If the alkoxy groups are substituted by alkoxy groups, then the methoxyethoxy or ethoxyethoxy group are preferred. If the alkoxy groups are substituted by amino groups, then the 2-aminoethoxy and 3-aminopropyloxy group are preferred.

If R^6 in the general formula I denotes an aryl or heteroaryl group substituted with an alkenyloxy residue, then straight-chained or branched residues with 3 to 6 carbon atoms, preferably the allyloxy group, are to be understood thereunder.

If R^6 in the general formula I denotes an aryl or heteroaryl group substituted with an alkynyloxy residue, then straight-chained or branched residues with 1 to 6 carbon atoms, preferably the propargyloxy group, are to be understood thereunder.

If R^6 in the general formula I denotes an aryl or heteroaryl group substituted with an alkylthio, alkylsulphinyl or alkylsulphonyl residue, then straight-chained or branched residues with 1 to 6 carbon atoms, preferably the methylthio, methylsulphinyl or methylsulphonyl group, are to be understood thereunder.

If R^6 in the general formula I denotes an aryl or heteroaryl group substituted with an alkylamino or dialkylamino residue, then straight-chained or branched residues with 1 to 6 carbon atoms, preferably the methylamino, dimethylamino or diethylamino group, are to be understood thereunder.

If R^6 in the general formula I denotes an aryl or heteroaryl group substituted with an alkylsulphonylamino residue, then straight-chained or branched residues

with 1 to 6 carbon atoms, preferably the methylsulphonylamino group, are to be understood thereunder.

If R^6 in the general formula I denotes an aryl or heteroaryl group substituted with an alkylcarbonylamino residue, then straight-chained or branched residues with 1 to 6 carbon atoms, preferably the acetylamino group, are to be understood thereunder.

If R^6 in the general formula I denotes an aryl or heteroaryl group substituted with an alkylaminocarbonyl or dialkylaminocarbonyl residue, then straight-chained or branched residues with 1 to 6 carbon atoms, preferably the methylaminocarbonyl, dimethylaminocarbonyl and the diethylaminocarbonyl group, are to be understood thereunder.

The benzyl group is particularly preferred under the aralkyl groups for R^6 and R^7.

As aryl residues R^6 or R^7, alone or linked with an alkyl chain, are to be understood aromatic hydrocarbons with 6 - 14 C atoms, especially the phenyl, the biphenyl, the naphthyl, tetrahydronaphthyl, indanyl or the fluorenyl residue.

As heteroaryl residue for R^6 are to be understood mono-, bi- and tricyclic aromatics with heteroatoms such as nitrogen, oxygen and sulphur, for example furan, thiophene, pyrrole, oxazole, isoxazole, thiazole, isothiazole, imidazole, pyrazole, triazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazine, tetrazine, benzothiophene, dibenzothiophene, benzimidazole, carbazole, benzofuran, benzofurazan, benzo-2,1,3-thiadiazole, quinoline, isoquinoline, quinazoline.

By the alkylene group Y in the general formula I, one understands linear or branched carbon chain with 1 to 6 carbon atoms, preferably the methylene, ethylene or propylene group.

If the substituents R^8 and R^9, together with the nitrogen atom to which they are bound, form a ring, then rings with 4 to 7 members are to be understood thereunder, especially the pyrrolidine, the piperidine and the homopiperidine ring. If this ring contains additional heteroatoms, then the morpholine, thiomorpholine and the piperazine ring are preferred thereunder.

The residue R^2 on the phenyl ring of the general formula I can stand in any desired positions in relation to the fragment X (oxygen atom or NH group). However, a configuration is particularly preferred in which all three substituents of the phenyl ring of the formula I are in meta position to one another.

R^1 denotes, in particular, the groups R^6-SO_2-NR^7-, R^6-NR^7-SO_2-, R^6-SO_2-0- or R^6-0-SO_2-.

R^2 denotes, in particular, a hydrogen, chlorine or bromine atom, or a C_1-C_6 alkyl group, such as e.g. a methyl or ethyl group, or a C_1-C_6-alkoxy group, such as e.g. the methoxy group or the trifluoromethyl group.

X is especially an oxygen atom or the NH group.

R^3 and R^4 can be the same or different and preferably represent hydrogen atoms or C_1-C_6 alkyl groups, especially hydrogen atoms or the methyl group.

R^5 is, in particular, a hydrogen atom, a C_2-C_6 alkyl group (such as e.g. a methyl group) or the benzyl group.

R^6 is, in particular, a C_1-C_6 alkyl group (such as e.g. the isopropyl group), a C_3-C_7 cycloalkyl group (such as e.g. the cyclopentyl or cyclohexyl group), a phenyl group, unsubstituted or substituted one or more times by fluorine, chlorine, C_1-C_6 alkyl (such as e.g. methyl, ethyl, tert.butyl), C_1-C_6 alkoxy (such as e.g. methoxy), nitro, amino, hydroxy, carboxy, benzyloxycarbonyl, C_1-C_6 alkoxycarbonyl (such as e.g. methoxy-

carbonyl), trifluoromethyl or the group -O-Y-CO_2R^8; a naphthyl, tetrahydronaphthyl, biphenyl or indanyl group, a thienyl, pyrazolyl or pyridyl group, a benzthienyl or benzothiadiazinyl group or the benzyl group.

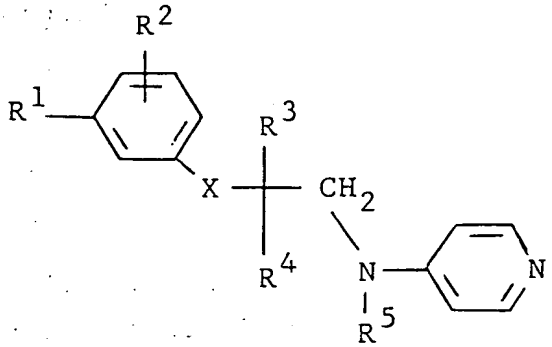
R^7 is, in particular, a hydrogen atom, a C_1-C_6 alkyl or C_2-C_6 alkenyl group (such as e.g. a methyl, ethyl, n-propyl, allyl, i-propyl group) or an aralkyl group (such as e.g. the benzyl group), a C_1-C_6 alkoxycarbonyl group (such as e.g. the ethoxycarbonyl group), a cyanoalkyl group (such as e.g. the cyanomethyl group), a hydroxyalkyl group (such as e.g. the hydroxyethyl or dihydroxypropyl group), or an aminoalkyl group (such as e.g. the aminomethyl group), a group -Y-COR^8 or a group -Y-$CONR^8R^9$.

Y is, in particular, a methylene, propylene, butylene or pentylene group.

R^8 is, in particular, a hydrogen atom or an alkyl group (such as e.g. the methyl or ethyl group), a hydroxyalkyl group (such as e.g. the hydroxyethyl, hydroxypropyl or dihydroxypropyl group) or an aminoalkyl group (such as e.g. the aminoethyl group).

R^9 is, in particular, a hydrogen atom or an alkyl group (such as e.g. the methyl group).

Compounds of the general formula I are preferred



(I)

in which

R^1 denotes the groups R^6-SO_2-NR^7-, R^6-NR^7-SO_2-, R^6-SO_2-0- or R^6-0-SO_2-,

R^2 denotes a hydrogen, chlorine or bromine atom, a methyl, ethyl, methoxy or the trifluoromethyl group,

X denotes an oxygen atom or the NH group,

R^3 and R^4 are the same or different and denote hydrogen atoms or methyl groups,

R^5 denotes a hydrogen atom, a methyl or benzyl group,

R^6 denotes an isopropyl, cyclopentyl or cyclohexyl group, a phenyl group, unsubstituted or substituted one or more times by fluorine, chlorine, methyl, ethyl, tert.butyl, methoxy, nitro, amino, hydroxy, carboxy, benzyloxycarbonyl, methoxycarbonyl, trifluoromethyl or the group -0-Y-CO_2R^8; a naphthyl, tetrahydronaphthyl, biphenyl or indanyl group, a thienyl, pyrazolyl or pyridyl group, a benzthienyl or benzothiadiazinyl group or the benzyl group,

R^7 denotes a hydrogen atom, a methyl, ethyl, n-propyl, allyl, i-propyl or a benzyl group, an ethoxycarbonyl, hydroxyethyl, dihydroxypropyl, cyanomethyl or aminoethyl group, a group -Y-COR^8 or a group -Y-$CONR^8R^9$,

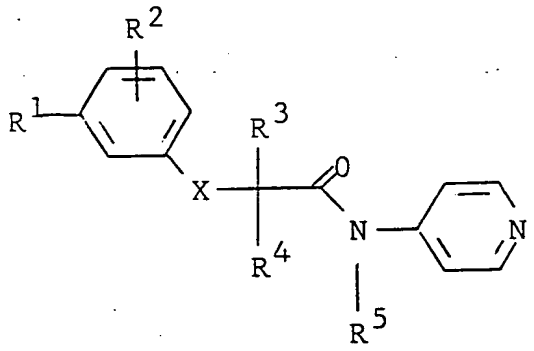
Y denotes a methylene, propylene, butylene or pentylene group,

R^8 denotes a hydrogen atom or a methyl, ethyl, hydroxyethyl, hydroxypropyl, dihydroxypropyl or aminoethyl group,

R^9 denotes a hydrogen atom or a methyl group.

The preparation of compounds of the general formula I takes place according to per se known methods.

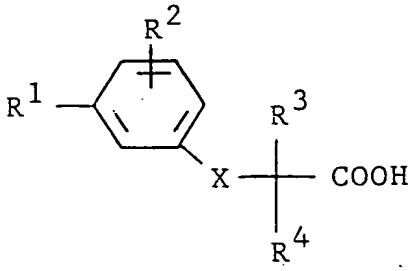
One starts from compounds of the general formula II,



(II)

which one reduces according to conventional methods. Complex boron and aluminium hydrides, boron hydride complexes, aluminium hydride, which one prepares in situ by reaction of $LiAlH_4$ with $AlCl_3$ or H_2SO_4, or a mixture of $AlCl_3$ and $NaBH_4$ come into consideration as reducing agents.

One prepares compounds of the general formula II by reaction of compounds of the general formula III

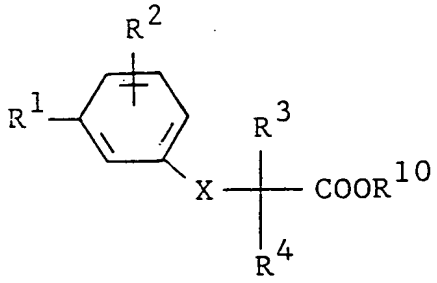


(III)

with 4-aminopyridine, the amino N atom of which carries the residue R^5. This reaction takes place by reaction of equimolar amounts of 4-aminopyridine and of the carboxylic acid of the general formula III in the presence of a dehydrating agent, such as polyphosphoric acid, an acidic cation exchanger, sulphuric acid halide, 2-halopyridinium salt, dicyclohexyl-carbodiimide or N,N'-carbonyldiimidazole. One can also allow this reaction to proceed in two steps, whereby one first converts the carboxylic acid into a reactive derivative e.g. an acid chloride, an acid azide or imidazolide and

then brings to reaction with the 4-aminopyridine.

One produces the carboxylic acids of the general formula III from the esters of the general formula IV

(IV) 

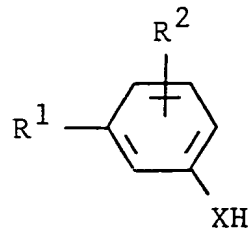
in which R^{10} denotes an alkyl or benzyl group. Depending upon the nature of this group, the reaction takes place either with the help of bases or acids or hydrogenolytically. If R^{10} is a methyl or ethyl group, then the reaction preferably takes place with sodium hydroxide solution or potassium hydroxide solution in methanol, ethanol or in water. If R^{10} is a tert.butyl group, then the reaction takes place with an acid, preferably hydrochloric acid, formic acid or trifluoroacetic acid. If R^{10} is a benzyl group, then the reaction preferably takes place hydrogenolytically in the presence of a catalyst, such as palladium on charcoal or with platinum.

One can produce another compound of the general formula IV, in which R^1 denotes the group R^6-$NR^{7'}$-SO-, R^6-$NR^{7'}$-SO_2-, R^6-SO-$NR^{7'}$- or R^6-SO_2-$NR^{7'}$-, by alkylation from compounds of the general formula IV, in which R^1 denotes the group R^6-NH-SO-, R^6-NH-SO_2-, R^6-SO-NH- or R^6-SO_2-NH-. As alkylating agents, one uses compounds of the general formula $R^{7'}$-Z, whereby $R^{7'}$ has the same meaning as R^7 with the exception of the hydrogen atom, the phenyl and heteroaryl group and Z denotes a reactive group, such as halogen, preferably bromine, chlorine or a sulphate. These reactions are preferably carried out in a solvent, such as acetone, ether, toluene or dimethylformamide at temperatures between -30°C and

100°C, preferably at room temperature, in the presence of a base, such as sodium hydride or calcium carbonate.

One prepares the compounds of general formula IV from the compounds of the general formula V

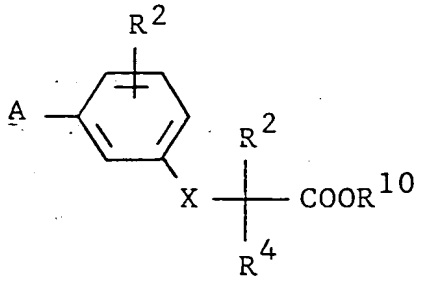
(V)



which one reacts with α-halogen esters of the general formula Hal-CR^3R^4-CO_2R^{10}. By Hal is to be understood a halogen atom, preferably chlorine and bromine. These reactions are preferably carried out in a solvent, such as acetone, ether, toluene or dimethylformamide, at temperatures between -30°C and 100°C, preferably at room temperature, in the presence of a base, such as sodium hydride or calcium carbonate.

One prepares the compounds of the general formula IV, in which R^1 denotes the group R^6-SO-O-, R^6-SO_2-O-, R^6-SO-NH- or R^6-SO_2-NH-, from the compounds of the general formula VI

(VI)

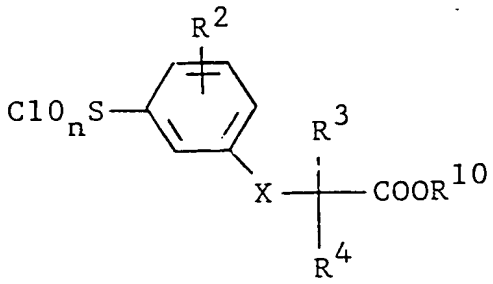


in that one reacts these with a sulfinyl chloride R^6-SOCl or sulfonyl chloride R^6-SO_2Cl. A thereby denotes a hydroxy or amino group NHR^7. The reaction expediently takes place with the addition of an acid-binding agent, such as e.g. alkali metal acetate, alkali metal hydroxide, calcium oxide, calcium carbonate, magnesium carbonate or with organic bases,

such as pyridine, triethylamine, N-methylmorpholine or diisopropylmethylamine, whereby e.g. ether, methylene chloride, dioxane, toluene or an excess of the tertiary amine serve as inert solvent. In the case of the use of inorganic acid binding agents, one uses e.g. water, aqueous ethanol or aqueous dioxane as a reaction medium.

One can prepare the compounds of the general formula IV, in which R^1 denotes the group R^6-0-SO-, R^6-0-SO_2-, R^6-NR^7-SO- or R^6-NR^7-SO_2-, from the compounds of the general formula VII

(VII)



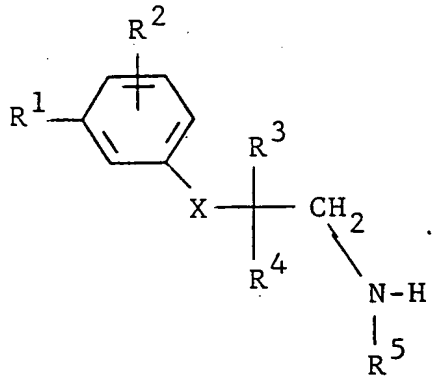
in which n equals one (sulfinyl chlorides) or equals 2 (sulfonyl chlorides). One reacts with compounds of the general formula R^6-OH or R^6-NH-R^7. The reaction expediently takes place with the addition of an acid-binding agent, such as e.g. alkali metal acetate, alkali metal hydroxide, calcium oxide, calcium carbonate, magnesium carbonate, or with organic bases, such as pyridine, triethylamine, N-methylmorpholine or diisopropylmethylamine, whereby e.g. ether, methylene chloride, dioxane, toluene or an excess of the tertiary amine serve as an inert solvent. In the case of the use of inorganic acid-binding agents, one uses e.g. water, aqueous ethanol or aqueous dioxane as a reaction medium.

The compounds of the general formula V and VII are known from the literature (Methoden der Organischen Chemie (Houben-Weyl), Thieme Verlag, Stuttgart 1955, p. 285; M. Quaedvlieg, Aliphatische Sulfinsäuren, p. 299; F. Muth, Aromatische Sulfinsäuren, p. 343;

M. Quaedvlieg, Aliphatische Sulfonsäuren, p. 429; F. Muth, Aromatische Sulfonsäuren, p. 599; F. Muth, Funktionelle N-Derivate der Arylsulfonsäuren, p. 659; F. Muth, Aromatische Sulfonsaureester) or can be produced according to the methods described there. The compounds of the general formula VI are known from the literature (Sobotka, Austin J. Am. Chem. Soc. 74, 3813 (1952)) or they can be produced according to methods described there.

A further method for the production of compounds of the general formula I consists in the reaction of compounds of the general formula VIII

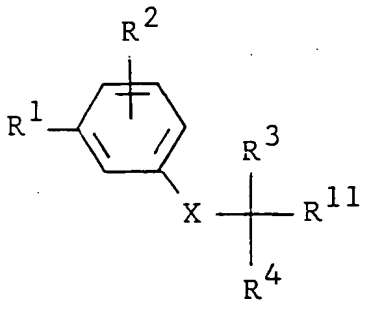
(VIII)



with a pyridine derivative which has a nucleophilic leaving group in position 4. Halogens, preferably bromine, chlorine and fluorine, as well as nitro, alkoxy and phenoxy groups come into consideration as such leaving groups. For the facilitation of the reaction, the 4-aminopyridine derivative can contain further halogen atoms, preferably chlorine. Preferred derivatives are pentachloropyridine and 4-nitro-tetrachloropyridine. One preferably carries out this reaction in an inert solvent, such as e.g. toluene, dioxane, dimethylformamide, dimethylacetamide, methylene chloride or ethanol, at temperatures between room temperature and boiling temperature of the solvent, preferably between 20 and 40°C. If the pyridine derivative contains further chlorine atoms, then the nucleophilic reaction is followed by a dehalogenation reaction, e.g. by catalytic hydrogenation.

One produces the compounds of the general formula VIII by reduction of compounds of the general formula IX

(IX)

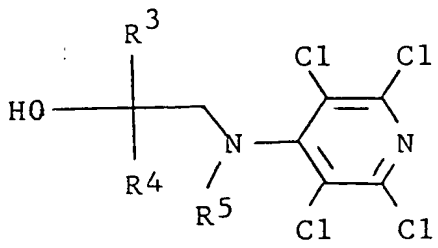


in which R^{11} denotes a nitrile group or an amide group $CONHR^5$. Complex boron and aluminium hydrides, boron hydride complexes, aluminium hydride, which one produces in situ reaction of $LiAlH_4$ with $AlCl_3$ or sulphuric acid, or a mixture of $AlCl_3$ and $NaBH_4$ come into consideration as the reducing agent.

One prepares the compounds of the general formula IX from the compounds of the general formula III. This reaction takes place by reacting equimolar amounts of an amine H_2NR^5 and of the carboxylic acid of the general formula III in the presence of a dehydrating agent, such as polyphosphoric acid, an acid cation exchanger, sulphuric acid halide, 2-halopyridinium salt, dicyclohexylcarbodiimide or N,N'-carbonyldiimidazole. One can also allow this reaction to proceed in two steps whereby one first converts the carboxylic acid into a reactive derivative, e.g. as acid chloride or an acid azide, and then brings to reaction.

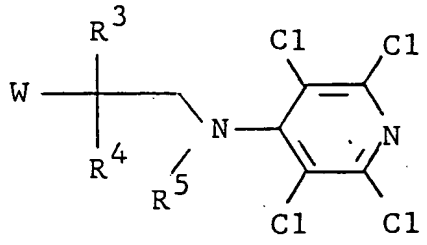
A further process for the production of compounds of the general formula I starts from the compounds of the general formula X

(X)



which one obtains according to methods known from the literature (M.M. Boudakian, in Heterocyclic Compounds, Vol. 14, Suppl. Part 2, (R.A. Abramovitch, ed.), Wiley, New York 1974, page 407) by reaction of the commercially available aminoethanols $HO-CR^3R^4-CH_2-NHR^5$ with pentachloropyridine or 4-nitrotetrachloropyridine in an inert solvent, such as dioxane, tetrahydrofuran, methylene chloride or ethanol, at temperatures between -10°C and the boiling temperature of the solvent. One converts the hydroxy group of compounds of the general formula X into a leaving group W and hereby obtains the compounds of the general formula XI

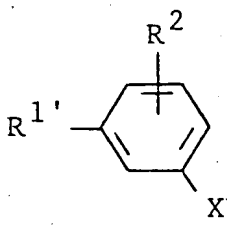
(XI)



in which W denotes a halogen atom, such as chlorine or bromine, or a sulfonic acid ester, such as tosyloxy. The conversion of the hydroxy group into a halogen atom takes place with a halogenation agent, such as thionyl chloride or phosphoryl chloride, the conversion into a sulfonic acid ester by reaction with a sulfonyl chloride, such as tosyl chloride.

One now reacts the compounds of the general formula XI with compounds of the general formula V'

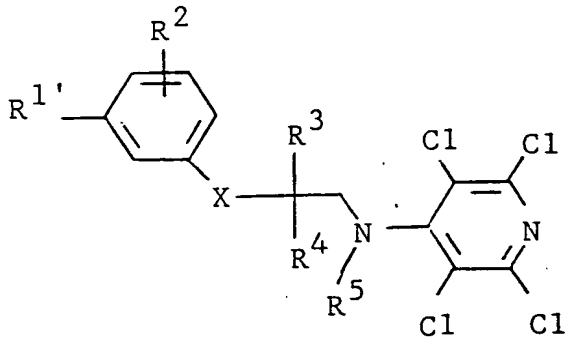
(V')



in which $R^{1'}$ has the same meaning as R^1 but, in addition,

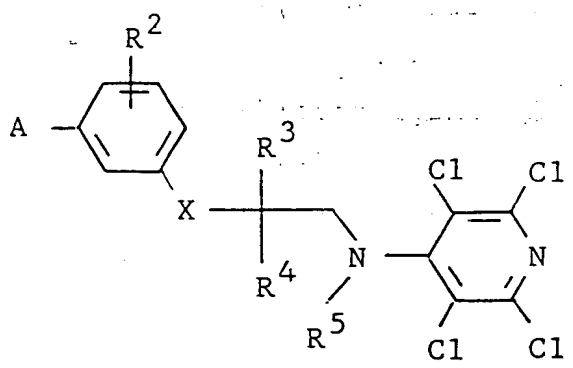
can also be a protected hydroxy group or amino group. By a protected hydroxy group, one understands the benzyloxy group of the acetyloxy group. By a protected amino group, one preferably understands the tert.butyloxycarbamoyl group, benzyloxycarbamoyl group, dibenzylamino group or the phthalimido group. There thereby result the compounds of the general formula XII. The reaction of compounds of the general formula V' with compounds of the general formula X instead of XI according to Mitsunobu in the presence of triphenylphosphine and diazodicarboxylic acid diethyl ester or piperidide also leads to compounds of the general formula XII.

(XII)



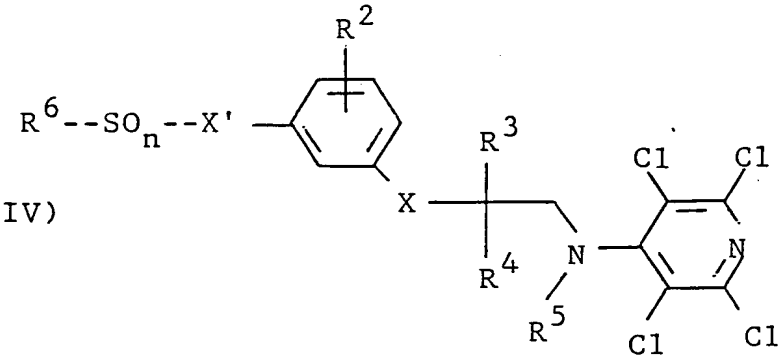
If $R^{1'}$ in the compounds of the general formula XII is a protected hydroxy group or a protected amino group, then the protecting group is removed in the next step. This takes place by hydrogenolysis in the presence of a catalyst, such as palladium on charcoal, for the benzyl protecting group, by a strong acid, such as trifluoroacetic acid, for the tert.butylcarbamoyl group and by a base, such as aqueous sodium hydroxide solution for the acetyl group. There thereby result compounds of the general formula XIII,

(XIII)



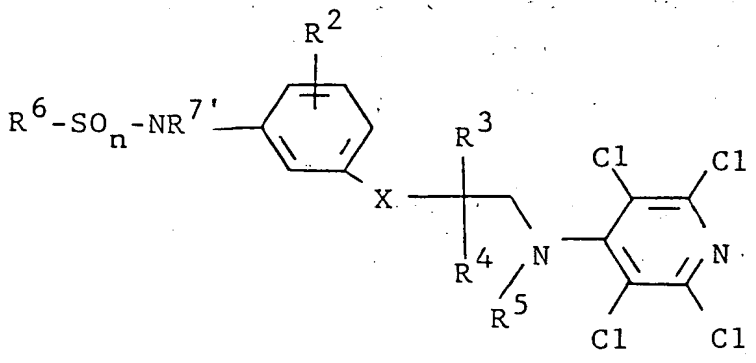
which one converts into the compounds of the general formula XIV by reaction with sulphinyl chlorides or sulphonyl chlorides

(XIV)



in which n can equal 1 or 2 and X' denotes the oxygen atom or the imino group NH. If X' denotes an imino group, then compounds of the general formula XIV are now converted into the compounds of the general formula XV

(XV)

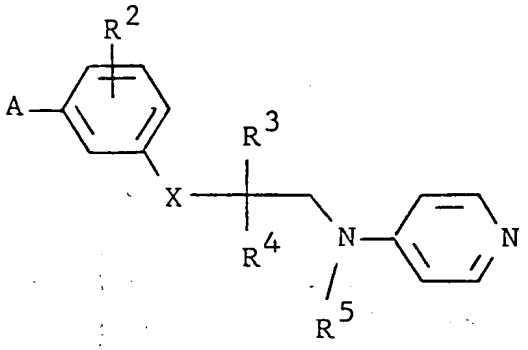


in which $R^{7'}$ has the same meaning as R^7 with the exception of the hydrogen atom. This takes place by reaction with alkylating agents $R^{7'}$-Y as is described in the case of alkylations of the general formula IV.

Finally, one obtains the compounds of the general formula I from the compounds of the general formula XII, in which $R^{1'}$ has the same meaning as R^1, from the compounds of the general formula XIV or from the compounds of the general formula XV by removal of the chlorine atoms of the pyridine ring. This takes place by catalytic hydrogenation in the presence of a catalyst, such as Raney nickel or palladium on charcoal, in the presence of a base, such as potassium carbonate, sodium hydrogen carbonate or sodium methylate.

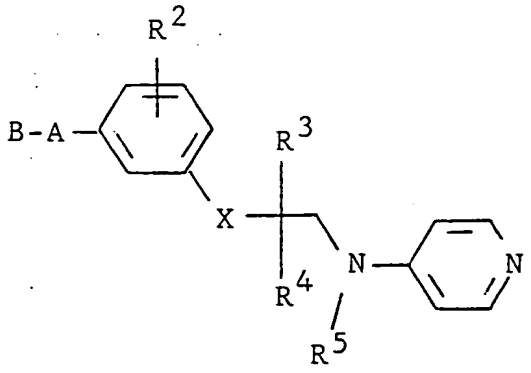
Another synthetic pathway for the production of compounds of the general formula I, in which R^1 denotes a R^6-SO-NR^7, R^6-SO_2-NR^7, R^6-SO-O- or R^6-SO_2-O group, consists in the reaction of compounds of the general formula XVI

(XVI)



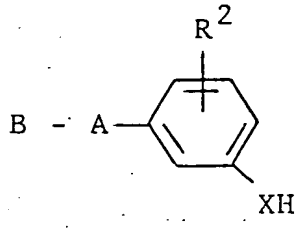
with a sulphinyl chloride R^6-SOCl or a sulphonyl chloride R^6-SO_2-Cl. The reaction takes place as described for the reaction with compounds of the general formula VI. A thereby denotes the hydroxy group or an amino group NHR^7.

One produces compounds of the general formula XVI from the compounds of the general formula XVII,

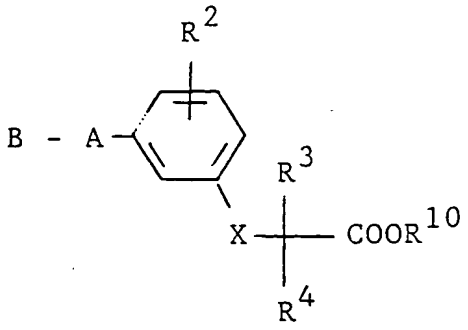
(XVII) 

in which B denotes a protecting group which is split off for the production of compounds of the general formula XVI. As protecting groups, there come into question the benzyl group, which one removes hydrogenolytically in the presence of a catalyst, such as palladium on charcoal, the tert.butyloxycarbonyl group, which one removes by the action of acids, such as trifluoroacetic acid, formic acid or hydrochloric acid, or an aromatic sulphonyl group, such as the benzenesulphonyl or tosyl group, which one removes by action of alkali, such as aqueous sodium hydroxide solution or aqueous potassium hydroxide solution.

One produces compounds of the general formula XVII according to the same principles as compounds of the general formula I. One preferably starts from compounds of the general formula XVIII,

(XVIII) 

which one reacts with halogen esters of the general formula Hal-CR^3R^4-CO_2R^{10} as is described for reactions with compounds of the general formula V. There thereby result compounds of the general formula XIX,

(XIX) 

which, after saponification of the ester and activation of the acidic functional group, one reacts with 4-aminopyridine or N-R^5-4-aminopyridine to give compounds of the general formula XVI as described in the case of compounds of the general formula III.

Certain compounds of the general formula I can be subsequently converted into other compounds of the general formula I.

This applies to compounds of the general formula I in which the group R^5, R^6 or R^7 denotes the benzyl group or in which R^6 denotes an aryl or heteroaryl group which, as substituents, carry one or more benzyloxy, benzylamino or benzyloxycarbonyl groups.

By catalytic hydrogenation in the presence of a catalyst, preferably palladium on charcoal, the benzyl group is thereby replaced by the hydrogen atom. The removal of the benzyl group also takes place by reaction with a strong acid, such as trifluoroacetic acid, in the presence of mesitylene, anisole or thioanisole.

This also applies to compounds of the general formula I in which R^6 denotes an aryl or heteroaryl group which, as substituents, carry one or more chlorine atoms. By catalytic hydrogenation in the presence of a catalyst, preferably palladium on charcoal, the chlorine atom is thereby replaced by the hydrogen atom.

This also applies to compounds of the general formula I in which R^6 denotes an aryl or heteroaryl group which, as substituents, carry one or more nitro groups. The nitro group is thereby replaced by the amino group by catalytic hydrogenation in the presence of a catalyst, preferably palladium on charcoal.

This also applies to compounds of the general formula I in which R^6 denotes an aryl or heteroaryl group which carry an alkyloxycarbonyl, alkyloxycarbonylalkyl or alkyloxycarbonylalkyloxy group as substituents or the group R^7 denotes an alkoxycarbonylalkyl group. In this case, the free carboxylic acids can be produced from the alkoxycarbonyl groups by reaction with acids, such as hydrochloric acid, or bases such as aqueous sodium hydroxide solution. If one reacts these alkoxycarbonyl groups with an amine of the general formula NHR^8R^9, then a $CONR^8R^9$ group is formed from the alkoxycarbonyl group. If one treats these alkoxycarbonyl groups with a reducing agent, such as $LiAlH_4$, then the corresponding hydroxymethyl groups result therefrom.

This also applies to compounds of the general formula I in which R^6 denotes an aryl or heteroaryl group which carry one or more nitriles, cyanoalkyl, cyanoalkyloxy, formylamino, alkylcarbonylamino, aminocarbonyl, alkylaminocarbonyl groups or a group $-S-Y-CONHR^8$, $-O-Y-CONHR^8$, $NH-Y-CONHR^8$ as substituents or in which R^7 denotes a cyanoalkyl, aminocarbonylalkyl or the group $-Y-CONHR^8$. These groups can be reduced, preferably with $LiAlH_4$, whereby the corresponding aminomethyl compounds result.

Examples of physiologically usable salts of the compounds of formula I are salts with physiologically compatible mineral acids, such as hydrochloric acid, sulphuric acid, sulphurous acid or phosphoric acid,

or with organic acids, such as methanesulphonic acid, p-toluenesulphonic acid, acetic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid. The compounds of formula I with free carboxy group can also form salts with physiologically compatible bases. Examples of such salts are alkaline metal, alkaline earth metal, ammonium and alkylammonium salts, such as the sodium, potassium, calcium or tetramethylammonium salt.

The compounds of formula I can be solvated, especially hydrated. The hydration can take place in the course of the production or gradually as a result of hygroscopic properties of an initially anhydrous compound.

One comes to pure enantiomers of the compounds of the formula I either by racemate resolution (via salt formation with optically active acids or bases) or in that one uses optically-active starting materials in the synthesis.

For the production of medicaments, the substances of the general formula I are mixed with suitable pharmaceutical carrier substances, aroma, flavourings and colouring materials and formed, for example, as tablets or coated tablets or are suspended or dissolved in water or oil, e.g. olive oil, with addition of appropriate auxiliary substances.

The substances of the general formula I and their salts can be administered enterally or parenterally in a liquid or solid form. Water is preferably used as injection medium which contains the additives usual in the case of injection solutions, such as stabilisers, solubilisers or buffers. Such additives are e.g. tartrate and citrate buffer, complexing formers (such as ethylenediamine-tetraacetic acid and its non-toxic salts) and high molecular polymers, such as liquid

polyethyloxide, for viscosity regulation. Solid carrier materials are e.g. starch, lactose, mannitol, methylcellulose, talc, highly dispersed silicic acids, high molecular fatty acids (such as stearic acid), animal and vegetable fats and solid high molecular polymers (such as polyethylene glycols). Preparations suitable for oral administration can, if desired, contain flavourings and sweeteners.

The compounds are usually administered in amounts of 10 - 1500 mg per day, referred to 75 kg body weight. It is preferable to administer 1 - 2 tablets with a content of active substance of 5 - 500 mg 2 - 3 times per day. The tablets can also be retarded whereby only 1 - 2 tablets have to be administered per day with 20 - 700 mg active substance. The active substance can also be administered by injection 1 - 8 times per day or by continuous infusion, whereby 50 - 2000 mg per day usually suffice.

Apart from the compounds mentioned in the Examples, preferred in the meaning of the invention are the following:

1. Benzenesulphinic acid-1-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester
2. N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulphinamide
3. 3-{3-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenylaminosulphonyl}-phenoxyacetic acid
4. 2-{3-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenylaminosulphonyl}-phenoxyacetic acid
5. 3-{3-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenylaminosulphonyl}-phenoxyacetamide
6. N-(2-Hydroxyethyl)-3-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenylaminosulphonyl}-phenoxy-acetamide

7. N-(2,3-Dihydroxypropyl)-3-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenylaminosulphonyl}-phenoxy-acetamide
8. N-(2-Hydroxyethyl)-3-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyloxysulphonyl}-phenoxy-acetamide
9. 3-{3-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl-aminosulphonyl}-phenoxyacetic acid morpholide
10. Acetic acid 2-[2-(benzenesulphonyl-{3-methyl-5-[2-pyridin-4-ylamino)-ethoxy]-phenyl}-aminoacetyl-amino]-ethyl ester
11. Acetic acid 3-[2-(benzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-aminoacetyl-amino]-propyl ester
12. Acetic acid 2-[2-(2-methoxybenzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-aminoacetylamino]-ethyl ester
13. N-{3-Cyano-5-[2-pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulphonamide.

Example 1

N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-2-naphthalene-sulphonamide

a) One added 6.3 g (28 mmol) naphthalene-2-sulphonyl chloride in 10 ml methylene chloride dropwise at 10°C to 5.9 g (25 mmol) 3-aminophenoxyacetic acid ethyl ester and 6.9 ml triethylamine in 100 ml methylene chloride with ice cooling. One stirred for 1 h at room temperature, extracted with water and dried the organic phase over sodium sulphate. One removed the solvent in a vacuum and obtained 9.6 g N-{3-[(ethoxy-carbonyl)-methoxy]-phenyl}-2-naphthalene-sulphonamide as oil. MS m/e = 385.

b) One added 4.2 g (75 mmol) potassium hydroxide to 9.6 g (25 mmol) of this compound in 100 ml ethanol and stirred for 1 h at 70°C. One filtered, dissolved

the precipitate in water, acidified with conc. hydrochloric acid and extracted with ethyl acetate. One removed the solvent in a vacuum, dissolved the residue in 2 N aqueous sodium hydroxide solution, acidified with conc. hydrochloric acid and extracted with ethyl acetate. One dried the organic phase over sodium sulphate, filtered and removed the solvent in a vacuum. The oily residue crystallised on standing. One obtained 7.6 g (85%) N-{3-[(carboxy)-methoxy]-phenyl}-2-naphthalene-sulphonamide. M.p. 153 - 155°C. FAB-MS: M+H = 358.

c) One added 2.7 g. (16.8 mmol) 1,1-carbonyldiimidazole to 3 g. (8.4 mmol) of this compound in 30 ml tetrahydrofuran at 45°C and stirred for 20 minutes. To this one added 0.8 g (8.4 mmol) 4-aminopyridine and stirred for 6 hours at 60°C. One then again added 2.7 g (16.8 mmol) 1,1-carbonyldiimidazole and 0.8 g (8.4 mmol) 4-aminopyridine thereto and stirred for a further 6 h at 60°C. One removed the solvent in a vacuum, took up the residue in ethyl acetate and extracted with aqueous sodium bicarbonate and with phosphate buffer, pH = 7.0. One dried the organic phase with sodium sulphate, filtered and removed the solvent in a vacuum. One obtained 2.5 g (69%) N-{3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-2-naphthalene-sulphonamide. M.p. 204 - 207°C. MS m/e = 433.

d) One added 2.0 g (4.6 mmol) of this compound under nitrogen to 1.0 g (20.4 mmol) lithium aluminium hydride in 20 ml tetrahydrofuran and heated to the boil for 1 h under reflux. One decomposed excess $LiAlH_4$ with water, filtered and evaporated the filtrate in a vacuum. One took up the residue in ethyl acetate, extracted with water, dried the organic phase with sodium sulphate, filtered and removed the

solvent in a vacuum. One separated the oily residue via a reverse-phase column (RP-18; eluent: methanol/water pH = 6.3, 7:3). The desired fraction was evaporated to dryness in a vacuum and extracted with ethyl acetate. One dried the organic phase over sodium sulphate, filtered and removed the solvent in a vacuum. One obtained 0.3 g (16%) of the title compound with the m.p. 90 - 91°C.
MS m/e = 419.

Example 2

N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-1-naphthalene-sulphonamide

The preparation took place analogously to Example 1 except that in step a) 1-naphthalene-sulphonyl chloride was used instead of 2-naphthalenesulphonyl chloride.

Intermediate steps:

a) N-{3-[(Ethoxycarbonyl)-methoxy]-phenyl}-1-naphthalenesulphonamide as oil. MS m/e = 385.

b) N-{3-[(Carboxy)-methoxy]-phenyl}-1-naphthalene-sulphonamide. M.p. 147 - 149°C. FAB-MS: M+H = 358.

c) N-{3-[(Pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-1-naphthalenesulphonamide. M.p. 210 - 211°C (decomp.). MS m/e = 433.

d) Title compound. Yield 38%. M.p. 239 - 241°C (decomp.). MS: pos. LSIMS m/e = 419.

Example 3

4-Methyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy[-phenyl}-benzenesulphonamide

The preparation took place analogously to Example 1 except that in step a) 4-toluenesulphonyl chloride was used instead of 2-naphthalenesulphonyl chloride.

Intermediate steps:

a) 4-Methyl-N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulphonamide. M.p. 100 - 102°C. MS m/e = 349.

b) 4-Methyl-N-{3-[(carboxy)-methoxy]-phenyl}-benzenesulphonamide. M.p. 170 - 173°C. FAB-MS: M+H = 322.

c) 4-Methyl-N-{3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulphonamide as oil. MS m/e = 397.

d) Title compound. Yield 26%. M.p. 165 - 167°C. MS m/e = 383.

Example 4

4-Fluoro-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulphonamide-hydrochloride

The preparation took place analogously to Example 1 except that in step a) 4-fluorobenzenesulphonyl chloride was used instead of 2-naphthalenesulphonyl chloride.

Intermediate steps:

a) 4-Fluoro-N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulphonamide, M.p. 94 - 96°C. MS m/e = 353.

b) 4-Fluoro-N-{3-[(carboxy)-methoxy]-phenyl}-benzenesulphonamide. M.p. 154 - 156°C. FAB-MS: M+H = 326.

c) 4-Fluoro-N-{3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulphonamide. MS m/e = 401.

d) Title compound. The base was triturated with hydrochloric acid in ether: Yield 21%. M.p. 203 - 205°C. MS m/e = 387.

Example 5

4-Chloro-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulphonamide hydrochloride

The preparation took place analogously to Example 1 except that in step a) 4-chlorobenzene-

sulphonyl chloride was used instead of 2-naphthalene-sulphonyl chloride.

Intermediate steps:

a) 4-Chloro-N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulphonamide. MS m/e = 169.

b) 4-Chloro-N-{3-[(carboxy)-methoxy]-phenyl}-benzene-sulphonamide. M.p. 190 - 192°C. FAB-MS: M+H = 342.

c) 4-Chloro-N-{3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulphonamide. M.p. 168 - 171°C. MS m/e = 417.

d) 0.65 g (1.55 mmol) from step c) in 15 ml dry tetra-hydrofuran were mixed with 1.79 ml (3.58 mmol) 2 M borane dimethylsulphide in tetrahydrofuran. One stirred for 3 h at 60°C and 10 ml methanol added thereto in an ice bath. To this one added 5 ml hydrogen chloride in ether. One removed the solvent in a vacuum and triturated the residue with warm water. One obtained 0.13 g of the title compound with m.p. 241 - 243°C. MS m/e = 403.

Example 6

4-Trifluoromethyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulphonamide

The preparation took place analogously to Example 1 except that in step a) 4-trifluoromethyl-benzenesulphonyl chloride was used instead of 2-naphthalenesulphonyl chloride.

Intermediate steps:

a) 4-Trifluoromethyl-N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulphonamide. MS m/e = 403.

b) 4-Trifluoromethyl-N-{3-[(carboxy)-methoxy]-phenyl}-benzenesulphonamide. M.p. 155 - 158°C. FAB-MS: M+H = 375.

c) 4-Trifluoromethyl-N-{3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulphonamide. M.p. 66 - 68°C. MS m/e = 451.

d) Title compound m.p. 145 - 148°C. MS m/e = 437.

Example 7

3-Trifluoromethyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulphonamide

The preparation took place analogously to Example 1 except that 3-trifluoromethylbenzenesulphonyl chloride was used instead of 2-naphthalenesulphonyl chloride.

Intermediate steps:

a) 3-Trifluoromethyl-N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulphonamide. MS m/e = 403.

b) 3-Trifluoromethyl-N-{3-[(carboxy)-methoxy]-phenyl}-benzenesulphonamide. M.p. 147 - 149°C. FAB-MS: M+H = 375.

c) 3-Trifluoromethyl-N-{3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulphonamide as oil. MS m/e = 451.

d) Title compound. M.p. 185 - 187°C. MS m/e = 437.

Example 8

N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-cyclohexanesulphonamide

The preparation took place analogously to Example 1 except that in step a) cyclohexylsulphonyl chloride was used instead of 2-naphthalenesulphonyl chloride.

Intermediate steps:

a) N-{3-[(Ethoxycarbonyl)-methoxy]-phenyl}-cyclohexanesulphonamide. MS m/e = 341.

b) N-{3-[(Carboxy)-methoxy]-phenyl}-cyclohexanesulphonamide. M.p. 132°C. FAB-MS: M+H = 313.

c) N-{3-[(Pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-cyclohexanesulphonamide as oil. MS m/e = 189.

d) Title compound. MS m/e = 375.

Example 9

N-{3-[2-(Pyridin-4-ylamino)-methoxy]-phenyl}-benzenesulphonamide

The preparation took place analogously to Example 1 except that in step a) benzenesulphonyl chloride was used instead of 2-naphthalenesulphonyl chloride.

Intermediate steps:

a) N-{3-[(Ethoxycarbonyl)-methoxy]-phenyl}-benzenesulphonamide as oil. MS m/e = 335.

b) N-{3-[(Carboxy)-methoxy]-phenyl}-benzenesulphonamide. M.p. 160 - 161°C. FAB-MS: M+H = 307.

c) N-{3-[(Pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulphonamide. M.p. 151 - 156°C. MS m/e = 383.

d) Title compound. Yield 26%. M.p. 182 - 184°C. MS m/e = 369.

Example 10

N-{3-[1-Methyl-2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulphonamide

a) One added 5.6 ml (44 mmol) benzenesulphonyl chloride dropwise at 10°C to 8.4 f (40 mmol) 2-(3-aminophenoxy)-propionic acid ethyl ester and 6.1 ml (44 mmol) triethylamine in 50 ml methylene chloride with ice cooling. One stirred for 1 h at room temperature, extracted with water, dried the organic phase with sodium sulphate, filtered and removed the solvent in a vacuum. One obtained 14 g N-{3-[1-(ethoxycarbonyl)-ethoxy]-phenyl}-benzenesulphonamide as oil. MS m/e = 349.

b) One stirred 14 g (40 mmol) of this compound and 6.7 g (120 mmol) potassium hydroxide in 100 ml ethanol for 1 h at 70°C. One extracted twice with ethyl acetate, acidified with half-concentrated hydrochloric acid and again extracted with ethyl acetate. One dried the combined organic phases over sodium sulphate, filtered and removed the solvent in a vacuum. One obtained 9.2 g (72%) N-{3-[1-(carboxy)-ethoxy]-phenyl}-benzenesulphonamide as oil. MS m/e = 321.

c) One prepared 3.4 g (57%) N-{3-[1-(pyridin-4-ylamino-carbonyl)-ethoxy]-phenyl}-benzenesulphonamide, m.p. 142 - 144°C. MS m/e = 397, as in Example 1, step c) from 4.8 g (15 mmol) of this compound, 2.1 g (22.5 mmol) 4-aminopyridine and 3.2 g (19.5 mmol) 1,1-carbonyldiimidazole in 40 ml tetrahydrofuran.

d) One prepared 0.6 g (37%) of the title compound, m.p. 162 - 163°C. MS m/e = 383, from 1.7 g (4.3 mmol) of this compound and 0.65 g (17.2 mmol) lithium aluminium hydride in 20 ml tetrahydrofuran as in Example 1, step d).

Example 11

N-{3-[1,1-Dimethyl-2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulphonamide

The compound was prepared analogously to Example 10. One used 2-methyl-2-(3-aminophenoxy)-propionic acid ethyl ester in step a) instead of 2-(3-aminophenoxy)-propionic acid ethyl ester.

a) N-{3-[2-Methyl-1-(ethoxycarbonyl)-ethoxy]-phenyl}-benzenesulphonamide as oil. MS m/e = 363.

b) N-{3-[1-Methyl-(carboxy)-ethoxy]-phenyl}-benzene-sulphonamide as oil. MS m/e = 335.

c) N-{3-[1-Methyl-(pyridin-4-ylaminocarbonyl)-ethoxy]-phenyl}-benzenesulphonamide. M.p. 141 - 143°C. MS m/e = 411.

d) Title compound as oil. MS m/e = 397.

Example 12

N-Methyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulphonamide hydrochloride

a) One dropped a solution of 1.6 ml (25 mmol) iodomethane in 10 ml dimethylformamide at 80 - 90°C to 8.4 g (25 mmol) N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulphonamide (Example 9, step a) and 3.5 g potassium carbonate in 10 ml dimethylformamide. One stirred for a further 2 h at this temperature, allowed to cool to room temperature, filtered and evaporated the filtrate in a vacuum. One took up the residue in ethyl acetate and extracted with water. One dried over sodium sulphate, filtered and removed the solvent in a vacuum. One obtained 8.6 g N-methyl-N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulphonamide as oil. MS m/e = 349.

b) The further reaction took place as in Example 1, step b. One obtained N-methyl-N-{3-[(carboxy)-methoxy]-phenyl}-benzenesulphonamide, M.p. 110 - 111°C. MS m/e = 321.

c) N-Methyl-N-{3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulphonamide. M.p. 76 - 78°C. MS m/e = 397.

d) Title compound. One mixed the free base with 2N hydrochloric acid, extracted with ethyl acetate and evaporated the aqueous phase to dryness. One obtained an oil which crystallised after triturating with isopropanol. Yield 46%. M.p. 174 - 176°C.

Example 13

N-Ethyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulphonamide

The preparation took place analogously to Example 12 except that one used iodoethane instead of iodo-

methane in step a).

a) N-Ethyl-N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulphonamide as oil. MS m/e = 363.

b) N-Ethyl-N-{3-[(carboxy)-methoxy]-phenyl}-benzenesulphonamide. M.p. 122°C. MS m/e = 335.

c) N-Ethyl-N-{3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulphonamide. MS m/e = 411.

d) Title compound as oil. MS m/e = 397.

Example 14

N-Propyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulphonamide

The preparation took place analogously to Example 12 except that one used iodopropane instead of iodomethane in step a).

a) N-Propyl-N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulphonamide as oil. MS m/e = 377.

b) N-Propyl-N-{3-[(carboxy)-methoxy]-phenyl}-benzenesulphonamide. M.p. 147°C. MS m/e = 349.

c) N-Propyl-N-{3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulphonamide. M.p. 105°C. MS m/e = 425.

d) Title compound as oil. MS m/e = 411.

Example 15

N-Benzyl-N-{3-[2-(pyridin-4-ylamino)-methoxy]-phenyl}-benzenesulphonamide

The preparation took place analogously to Example 12 except that one used benzyl bromide instead of iodomethane in step a).

a) N-Benzyl-N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulphonamide as oil. MS m/e = 425.

b) N-Benzyl-N-{3-[(carboxy)-methoxy]-phenyl}-benzenesulphonamide. M.p. 190°C. MS m/e = 397.

c) N-Benzyl-N-{3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulphonamide. M.p. 140°C. MS m/e = 473.

d) Title compound. M.p. 128°C. MS m/e = 459.

Example 16

N-Allyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulphonamide

The preparation took place analogously to Example 12 except that one used allyl bromide instead of iodomethane in step a).

a) N-Allyl-N-{3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulphonamide as oil. MS m/e = 375.

b) N-Allyl-N-{3-[(carboxy)-methoxy]-phenyl}-benzenesulphonamide. MS m/e = 347.

c) N-Allyl-N-{3-[pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulphonamide. MS m/e = 423.

d) Title compound as oil. MS m/e = 409.

Example 17

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulphonamide hydrochloride

The preparation took place analogously to Example 12 except that, in step a), benzenesulphonyl chloride was used instead of 2-naphthalenesulphonyl chloride and 3-amino-5-methylphenoxyacetic acid ethyl ester instead of 3-aminophenoxyacetic acid ethyl ester.

Intermediate steps:

a) N-{5-Methyl-3-[(ethoxycarbonyl)-methoxy]-phenyl}-benzenesulphonamide as oil. MS m/e = 349.

b) N-{5-Methyl-3-[(carboxy)-methoxy]-phenyl}-benzenesulphonamide. M.p.: 156 - 159°C. FAB-MS: M+H = 322.

c) N-{5-Methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-benzenesulphonamide. M.p.: 193 - 196°C. MS m/e = 397

d) Title compound. Yield 56%. M.p. 170°C. MS m/e = 383.

Example 18

Benzenesulphonic acid 3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

a) One adds 0.44 g (0.11 mol) sodium hydride (60% in white oil) to 2.5 g (0.01 mol) benzenesulphonic acid 3-hydroxyphenyl ester in 30 ml acetonitrile while cooling at 10°C and stirs for 1 h at this temperature. One adds 2.2 ml (0.02 mol) ethyl bromoacetate in 10 ml acetonitrile dropwise within 10 minutes and stirs for 3 h at room temperature. After addition of 5 ml isopropanol, one removes the solvent in a vacuum. One adds 30 ml ethanol, 50 ml water and 0.8 g (0.015 mol) potassium hydroxide to the residue. After 16 h at room temperature, one removes the ethanol in a vacuum and extracts the aqueous solution three times with ether. One acidifies the aqueous phase with hydrochloric acid and extracts with ether. One removes the ether in a vacuum and obtains 1.5 g (48%) 2-[3-(phenylsulphonyloxy)-phenyloxy]-acetic acid with the m.p. 152 - 155°C.

b) One stirs 1.4 g (4.5 mmol) of this compound and 958 mg (5.9 mmol) carbonyldiimidazole for 30 min at 45°C. One adds thereto 0.64 g (6.8 mmol) 4-amino-pyridine and stirs for two days at 60°C. One removes the solvent in a vacuum and dissolves the residue in ethyl acetate which contained 0.5% acetic acid. One dries the organic phase, filters and removes the solvent in a vacuum. One triturates the residue with ether, filters and obtains 1.8 g (94%) N-(4-pyridinyl)-2-[3-(phenylsulphonyloxy)-phenyloxy]-acetamide with the m.p. 127 - 130°C.

c) One mixes 192 mg (8.8 mmol) lithium borohydride in 5 ml dry tetrahydrofuran at 5°C while cooling in an

ice bath, with 2.23 ml (18 mmol) chlorotrimethylsilane. After 30 minutes, one adds thereto slowly at 5°C 1.7 g (4.4 mmol) of the compound from step b). After 16 hours at room temperature, one decomposed with 3 ml methanol and removed the solvent in a vacuum. One takes up the residue in ethyl acetate and bicarbonate solution. One purifies the ethyl acetate phase via a silica gel column (ethyl acetate/methanol = 9:1). One removes the solvent in a vacuum and obtains 1.3 g of the title compound (80%) as viscous oil. FAB-MS: M+H 371.

Example 19

N-Methyl-N-phenyl-3-[2-(pyridin-4-ylamino)-ethoxy]-benzenesulphonamide

a) 3-Nitrobenzenesulphonic acid-N-methyl-anilide

5 g 3-nitrobenzenesulphonic acid chloride are dissolved in 20 ml absol. pyridine and mixed with 2.7 ml N-methylaniline with ice cooling and stirring. One further stirs for 2 hrs. at room temperature, adds the reaction mixture to ice water and acidifies with dilute hydrochloric acid. The aqueous phase is extracted with ethyl acetate, the ethyl acetate phase dried over sodium sulphate and evaporated. The residue is recrystallised from alcohol. Yield: 6.3 g. M.p. 90°C.

b) 3-Aminobenzenesulphonic acid-N-methyl-anilide

6 g 3-nitrobenzenesulphonic acid-N-methylanilide are dissolved in 100 ml absol. tetrahydrofuran and hydrogenated after addition of 0.5 g Pd/C (10%) catalyst. After take up of the calculated amount of hydrogen, it is filtered from the catalyst and the filtrate evaporated. Yield: 5.5 g. M.p. 104°C.

c) 3-Hydroxybenzenesulphonic acid-N-methyl-anilide

5 g 3-aminobenzenesulphonic acid-N-methylanilide are dissolved in 20 ml 50% sulphuric acid. One adds to this a solution of 1.75 g sodium nitrite in 5 ml water, with ice cooling and stirring. After ending of diazotisation, one heats the reaction mixture for 20 min. to 100°C, allows to cool and extracts with ethyl acetate. The ethyl acetate phase is dried over sodium sulphate and evaporated. The residue is sufficiently pure for the further processing.

d) [3-(Methylphenylsulphamoyl)-phenoxy]-acetic acid ethyl ester

3.5 g 3-hydroxybenzenesulphonic acid-N-methylanilide are dissolved in 20 ml absol. dimethylformamide. To this one adds 2 g potassium carbonate and 1.9 ml bromoacetic acid ethyl ester and heats the mixture for 3 hrs. to 100°C. One cools and distils off the solvent in a vacuum. The residue obtained (4.3 g) is sufficiently pure for the further processing.

e) [3-(Methylphenylsulphamoyl)-phenoxy]-acetic acid

4.2 g [3-(methylphenylsulphamoyl)-phenoxy]-acetic acid ethyl ester are dissolved in 40 ml ethanol. To this one adds 1 g potassium hydroxide and stirs the mixture for one hour at 90°C. One cools to room temperature, acidifies with dilute hydrochloric acid and extracts with methylene chloride. The methylene chloride phase is dried over sodium sulphate and evaporated. One obtains 4 g [3-(methylphenyl-sulphamoyl)-phenoxy]-acetic acid as amorphous solid.

f) 2-[3-(Methylphenylsulphamoyl)-phenoxy]-N-pyridin-4-yl-acetamide

2 g [3-(methylphenylsulphamoyl)-phenoxy]-acetic acid are dissolved in 20 ml absol. tetrahydrofuran. To this one adds 1.35 g carbonyldiimidazole and heats the mixture for 20 minutes to 45°C. One cools to

room temperature, adds 900 mg 4-aminopyridine thereto and further stirs for 3 hours at 60°C. One distils off the solvent, dissolves the residue in ethyl acetate and shakes out with water. The ethyl acetate phase is dried over sodium sulphate and evaporated. For purification, the residue is chromatographed on a silica gel column (eluting agent: methylene chloride/methanol 9:5). After evaporation of the column fractions, one obtains 1.5 g of the title compound as amorphous solid. FAB-MS: M+H = 398.

g) N-Methyl-N-phenyl-3-[2-(pyridin-4-ylamino)-ethoxy]-benzenesulphonamide

800 mg 2-[3-(methylphenylsulphamoyl)-phenoxy]-N-pyridin-4-yl-acetamide are dissolved in 15 ml absol. tetrahydrofuran. To this one adds 320 mg lithium aluminium hydride under nitrogen and subsequently heats the mixture for one hour to reflux temperature. One cools and decomposes the reaction batch with saturated ammonium sulphate solution. One filters off with suction from the insoluble material, washes the filter residue with ether, dries the filtrate over sodium sulphate and evaporates. For purification, the residue is chromatographed on a silica gel column (eluting agent: methylene chloride/methanol 8:2). After evaporation of the column fractions, one obtains 420 mg of the title compound as amorphous substance. FAB-MS: M+H 384.

Example 20

N-Benzyl-N-phenyl-3-[2-(pyridin-4-ylamino)-ethoxy]-benzenesulphonamide

The preparation of the title compound took place analogously to Example 19 except that N-benzylaniline was used in step a) instead of N-methylaniline. Amorphous substance. FAB-MS: M+H 460.

Example 21

N-Phenyl-3-[2-(pyridin-4-ylamino)-ethoxy]-benzene-sulphonamide

300 mg N-benzyl-N-phenyl-3-[2-(pyridin-4-ylamino)-ethoxy]-benzenesulphonamide (Example 20) are dissolved in 20 ml methanol and hydrogenated after addition of 100 mg Pd/C (10%) catalyst. After ending of the hydrogen uptake, it is filtered off from the catalyst and evaporated. One obtains 240 mg of the title compound as amorphous substance. FAB-MS: M+H 370.

Example 22

N-Methyl-N-pyridin-2-yl-3-[2-(pyridin-4-ylamino)-ethoxy]-benzenesulphonamide

The preparation of the title compound took place analogously to Example 19 except that N-methyl-2-aminopyridine was used in step a) instead of N-methyl-aniline. Amorphous substance. FAB-MS: M+H 385.

Example 23

N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-2-propanesulphonamide hydrochloride

To 0.26 g (11.4 mmol) $LiBH_4$ in 50 ml tetrahydrofuran are added dropwise 2.88 ml (22.9 mmol) chlorotrimethylsilane, stirred for 5 min. at room temperature and added portionwise thereto 2.00 g (5.72 mmol) N-{3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-2-propanesulphonamide which one had prepared analogously to Example 1. One heated for 30 minutes under reflux, after cooling carefully added 20 ml methanol thereto dropwise, followed by 30 ml 2 N sodium hydroxide solution. One removed the solvent to the greater part in a vacuum and extracted with methylene chloride. One dried, removed the solvent in a vacuum and mixed the residue with ethereal hydrochloric acid. One removed the solvent in a vacuum, triturated the residue with tert.butyl methyl ether and obtained 1.5 g (70%) of the title compound with the m.p. 204 - 207°C.

Example 24

N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-cyclopentanesulphonamide hydrochloride

was prepared analogously to Example 23. M.p. 129 - 134°C.

Example 25

N-Methyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-4-fluorophenylsulphonamide hydrochloride

was prepared analogously to Example 23. M.p. 140 - 143°C.

Example 26

N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulphonamide

was prepared analogously to Example 1. Oil.
MS: [EI] = 383.

Example 27

N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-4-tert. butylbenzenesulphonamide

was prepared analogously to Example 1. Oil.
MS: [EI] = 425.

Example 28

N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-1,2,3,4-tetrahydronaphthalene-6-sulphonamide hydrochloride

was prepared analogously to Example 23. M.p. 235 - 237°C.

Example 29

N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-indane-5-sulphonamide

was prepared analogously to Example 23 as a free base. M.p. 140°C (decomp.).

Example 30

N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-2-biphenylsulphonamide

was prepared analogously to Example 23 as a free base. M.p. 214 - 216°C.

Example 31

N-Methyl-N-{5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-4-fluorobenzenesulphonamide hydrochloride

was prepared analogously to Example 23. M.p. 122 - 129°C. One prepared the starting material N-{5-methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-4-fluorobenzenesulphonamide (MS m/e = 429) analogously to Example 17.

Example 32

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl -2-chloro-4-fluorobenzenesulphonamide hydrochloride

was prepared analogously to Example 23. M.p. 198 - 200°C. One prepared the starting material N-{5-methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-2-chloro-4-fluorobenzenesulphonamide (MS m/e = 449) analogously to Example 17.

Example 33

N-Methyl-N-{5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-trifluorobenzenesulphonamide hydrochloride

was prepared analogously to Example 23. M.p. 203 - 207°C. One prepared the starting material N-{5-methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-2-chloro-4-fluorobenzenesulphonamide (MS m/e = 479) analogously to Example 17.

Example 34

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-methylbenzenesulphonamide hydrochloride

was prepared analogously to Example 23. M.p. 135°C (decomp.). One prepared the starting material N-{5-

methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-2-methylbenzene-sulphonamide (MS m/e = 411) analogously to Example 17.

Example 35

N-Methyl-N-{5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-methyl-4-fluorobensenesulphonamide hydrochloride

was prepared analogously to Example 23. M.p. 146°C. One prepared the starting material N-methyl-N-{5-methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-2-methyl-4-fluorobenzenesulphonamide (MS m/e = 443) analogously to Example 17.

Example 36

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-methyl-4-fluorobenzenesulphonamide hydrochloride

was prepared analogously to Example 23. M.p. 193°C. One prepared the starting material N-{5-methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-2-methyl-4-fluorobenzenesulphonamide (MS m/e = 429) analogously to Example 17.

Example 37

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-methyl-5-fluorobenzenesulphonamide hydrochloride

was prepared analogously to Example 23. M.p. 246 - 247°C. One prepared the starting material N-{5-methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl -2-methyl-5-fluorobenzenesulphonamide (MS m/e = 429; m.p. 211 - 213°C) analogously to Example 17.

Example 38

N-Methyl-N-{5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-methyl-5-fluorobenzenesulphonamide hydrochloride

was prepared analogously to Example 23. M.p. 165 - 166°C.

One prepared the starting material N-methyl-N-{5-methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-2-methyl-5-fluorobenzenesulphonamide (MS m/e = 443) analogously to Example 17.

Example 39

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2,4-difluorobenzenesulphonamide hydrochloride

was prepared analogously to Example 23. M.p. 227 - 228°C. One prepared the starting material N-{5-methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-2,4-difluorobenzenesulphonamide (MS m/e = 433; M.p. 194°C) analogously to Example 17.

Example 40

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-3,5-dimethyl-4-pyrazolesulphonamide

was prepared analogously to Example 23 as a free base. M.p. 121°C. One prepared the starting material N-{5-methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-3,5-dimethyl-4-pyrazolesulphonamide (MS m/e = 415) analogously to Example 17.

Example 41

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-4-fluorobenzenesulphonamide hydrochloride

was prepared analogously to Example 23. M.p. 232°C. One prepared the starting material N-{5-methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-4-fluorobenzenesulphonamide (MS m/e = 415; m.p. 156 - 159°C) analogously to Example 17.

Example 42

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-fluorobenzenesulphonamide hydrochloride

was prepared analogously to Example 23. M.p. 263°C. One prepared the starting material N-{5-methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-2-fluorobenzenesulphonamide (MS m/e = 415) analogously to Example 17.

Example 43

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-trifluoromethylbenzenesulphonamide hydrochloride

was prepared analogously to Example 23. M.p. 217 - 222°C. One prepared the starting material N-{5-methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-2-trifluoromethylbenzenesulphonamide (MS m/e = 465) analogously to Example 17.

Example 44

N-Methyl-N-{5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-4-methylbenzenesulphonamide hydrochloride

was prepared analogously to Example 23. M.p. 180°C. One prepared the starting material N-methyl-N-{5-methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-4-methylbenzenesulphonamide (MS m/e = 425) analogously to Example 17.

Example 45

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2,6-difluorobenzenesulphonamide hydrochloride

was prepared analogously to Example 23. M.p. 263°C. One prepared the starting material N-{5-methyl-3-[(pyridin-4-ylaminocarbonyl)-methoxy]-phenyl}-2,6-difluorobenzenesulphonamide (MS m/e = 433; m.p. 234 - 242°C) analogously to Example 17.

Example 46

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-hydroxy-3-tert.butyl-5-methylbenzenesulphonamide hydrochloride

a) One mixed 27.2 g (87.0 mmmol) (3-tert.butyloxy-carbonylamino-5-methylphenoxy)-acetic acid ethyl ester (Example 57b) in 300 ml methanol with 50 ml (100 mmol) 2N sodium hydroxide solution and stirred for 3 d at room temperature. One partially removed the solvent in a vacuum, extracted with ethyl acetate,

acidified the aqueous phase with hydrochloric acid and extracted with ether. One dried and removed the solvent in a vacuum. One obtained 15.6 g (3-tert.butyloxycarbonylamino-5-methylphenoxy)-acetic acid with the m.p. 120 - 122°C.

b) One reacted this compound with 4-aminopyridine as described in Example 1c) and obtained N-(4-pyridinyl)-(3-tert.butyloxycarbonylamino-5-methylphenoxy)-acetamide with the m.p. 204 - 205°C.

c) One mixed 5.00 g (14.0 mmol) of this compound with 25 ml trifluoroacetic acid, stirred for 30 min. at room temperature, alkalised with sodium hydroxide solution and filtered off the precipitate with suction. One obtained 2.93 g (78%) N-(4-pyridinyl)-3-(amino-5-methylphenoxy)-acetamide with the m.p. 163°C.

d) One reduced this compound as described in Example 23 and obtained 3-[2-(pyridin-4-ylamino)-ethoxy]-5-methylaniline in 50% yield with the m.p. 208°C.

e) One reacted this compound with 2-hydroxy-3-tert.butyl-5-methylbenzenesulphonyl chloride as described in Example 1a) and obtained the tital compound. Amorphous. MS + FAB: 470.

Example 47

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-3-benzothiophene-sulphonamide hydrochloride

was prepared analogously to Example 46. For this purpose, one reacted the compound obtained in Example 46d) with benzothiophene-3-sulphonyl chloride. M.p. 130°C (decomp.).

Example 48

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzo-2,3,1-thiadiazole-4-sulphonamide hydrochloride

was produced analogously to Example 46. For this purpose, the compound obtained in Example 46d) was reacted with benzo-2,3,1-thiadiazole-4-sulphonyl chloride. M.p. 110°C.

Example 49

N-{5-Methoxy-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-4-fluorobenzenesulphonamide hydrochloride

a) One heated 16.0 g (115 mmol) 3-hydroxy-5-methoxy-phenol (G. Rodighiero, C. Antonello, Il Farmaco, Ed. Sci. 10, 889 - 896, (1955)), 3.7 g ammonium chloride, 13.8 ml water and 24 ml conc. ammonia in a 100 ml autoclave for 12 h to 130°C. After cooling, one rinsed out the autoclave contents with methanol, removed the solvent in a vacuum, triturated the residue with ethyl acetate, filtered off from insolubles (6.5 g), removed the solvent in a vacuum, applied the oily residue to a suction filter with silica gel and after-washed with heptane/ethyl acetate 1:1. One removed the solvent of the filtrate and obtained 10.4 g 3-hydroxy-5-methoxyaniline as red oil.

b) One acetylated this compound (10.4 g, 75.0 mmol) in 100 ml methylene chloride in the presence of 0.1 g 4-dimethylaminopyridine with 100 ml acetic anhydride for 12 h at room temperature. One removed the solvent in a vacuum, added 200 ml methanol and 20 ml saturated sodium carbonate solution to the residue (mainly diacetyl compound) and stirred for 3 h at room temperature. One removed the solvent in a vacuum, added 250 ml water thereto, acidified with conc. hydrochloric acid and extracted with ethyl acetate. Removal of the solvent yielded 11 g (81%) N-(3-hydroxy-5-methoxyphenyl)-acetamide with m.p. 126°C.

c) One alkylated this compound (11.0 g, 61.0 mmol) in 100 ml dry dimethylformamide in the presence of 9.1 g (65 mmol) potassium carbonate with 6.9 ml (65 mmol) chloroacetic acid ethyl ester for 8 h at 60°C. One diluted with water, acidified with hydrochloric acid and extracted with ethyl acetate. One extracted the organic phase with water, dried the organic phase over magnesium sulphate, filtered and removed the solvent in a vacuum. One obtained 10.8 g (66%) 2-(3-acetamido-5-methoxyphenoxy)-acetic acid ethyl ester as oil.

d) One stirred this compound (10.8 g, 40 mmol) in 70 ml ethanol for 4 h with 30 ml 2 N sodium hydroxide solution, removed the solvent in a vacuum, mixed with water and acidified. One filtered off the precipitate (5.5 g carboxylic acid) with suction, dissolved in 50 ml ethanol, added 50 ml 10 N sodium hydroxide solution thereto and boiled for 8 h under reflux. One acidified with conc. hydrochloric acid, removed the solvent in a vacuum, added 100 ml methanol thereto and stirred for 12 h at room temperature. One removed solvent in a vacuum, digested with ethyl acetate, filtered off with suction and obtained 5.6 g 2-(3-amino-5-methoxyphenoxy)-acetic acid methyl ester (MS, m/e = 211).

e) One obtained 2-[3-(4-fluorobenzenesulphonylamino)-5-methoxyphenoxy]-acetic acid methyl ester (MS m/e = 369) therefrom as oil by reaction with 4-fluorobenzenesulphonyl chloride as described in Example 1a).

f) One obtained 2-[3-(4-fluorobenzenesulphonylamino)-5-methoxyphenoxy)-acetic acid with the m.p. 161°C therefrom in a 95% yield as described in Example 1b).

g) One obtained N-(4-pyridinyl)-2-[3-(4-fluorobenzene-sulphonylamino)-5-methoxyphenoxy]-acetamide with the m.p. 161°C therefrom in a yield of 58% as described in Example 1c).

h) One obtained the title compound with the m.p. 62°C therefrom in a yield of 76% as described in Example 23.

Example 50

N-{3-[2-(Pyridin-4-ylamino)-ethoxy]-phenyl}-2-chlorobenzenesulphonamide

was prepared analogously to Example 1 in 58% yield. M.p. 221 - 223°C.

Example 51

N-Methyl-N-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl-2-chlorobenzenesulphonamide

was prepared analogously to Example 12 in 22% yield. M.p. 188 - 190°C.

Example 52

N-2-Propyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulphonamide

was prepared analogously to Example 12 in 47% yield. Oil. MS (m/e) = 411.

Example 53

N-Methyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-thiophenesulphonamide

was prepared analogously to Example 12 in 12% yield. M.p. 179 - 181°C.

Example 54

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-1-naphthalenesulphonamide hydrochloride

was prepared analogously to Example 17 in 14% yield. M.p. 215 - 218°C.

Example 55

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-thiophenesulphonamide hydrochloride

was prepared analogously to Example 17 in 24% yield. M.p. 252 - 254°C.

Example 56

N-{5-Methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-chlorobenzenesulphonamide hydrochloride

was prepared analogously to Example 17 in 42% yield. M.p. 254 - 258°C.

Example 57

N-Methyl-N-{5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-1-chlorobenzenesulphonamide hydrochloride

a) One mixes 96 g (0.78 mol 3-hydroxy-5-methylaniline (F. Wessely, H. Eibel, C. Friedrich, Monatshefte Chem. 83, 24 - 30, (1952)) in 1.2 l dioxane and 840 ml water with 420 ml 2 N sodium hydroxide solution and, with ice cooling, with 171 g (0.78 mol) ditert.butyldicarbonate. One stirred for 12 h at room temperature, removed the solvent in a vacuum, acidified to pH 2 - 3 with ice cooling and extracted with ethyl acetate. One dried the organic phase over sodium sulphate, filtered and removed the solvent in a vacuum. One obtained 174 g (quantitative) N-(tert.butyloxycarbonyl)-3-hydroxy-5-methylaniline as oil. MS (m/e) = 223.

b) One heated 132 g (0.59 mol) of this compound in 400 ml dry dimethylformamide, 90 g (0.65 mol) potassium carbonate and 69 ml (0.65 mol) chloroacetic acid ethyl ester for 3 h to 70°C. One shook into 1 l ice water, extracted with ethyl acetate, dried the organic phase over sodium sulphate, filtered and removed the solvent in a vacuum. One obtained 174 g

(95%) 2-(3-tert.butyloxycarbonylamino-5-methyl-phenoxy)-acetic acid ethyl ester as oil. MS (m/e) = 309.

c) With ice cooling, one mixed 174 g (0.562 mol) of this compound with 200 ml trifluoroacetic acid, stirred for 2 h at room temperature and removed the solvent in a vacuum. One mixed the residue with 2N hydrochloric acid, extracted with ethyl acetate, rendered the aqueous phase alkaline with sodium hydroxide solution and extracted with ethyl acetate. One dried the organic phase with sodium sulphate, filtered and removed the solvent in a vacuum. One obtained 87.5 g (74%) 2-(3-amino-5-methylphenyloxy)-acetic acid ethyl ester as oil. MS (m/e) = 209.

d) As described in Example 17a), one reacted this compound with 2-chlorobenzenesulphonyl chloride and obtained 2-[3-(2-chlorobenzenesulphonylamino)-5-methylphenoxy]-acetic acid ethyl ester with the m.p. 133 - 137°C in 56% yield.

e) One methylated this compound as described in Example 12a) and obtained N-methyl-2-[3-(2-chlorobenzenesulphonylamino)-5-methylphenoxy]-acetic acid ethyl ester in quantitative yield. Oil. MS (m/e) = 398.

f) One saponified this compound as described in Example 1b) and obtained N-methyl-2-[3-(2-chlorobenzenesulphonylamino)-5-methylphenoxy]-acetic acid in quantitative yield. M.p. 113 - 115°C.

g) One reacted this compound with 4-aminopyridine as described in Example 1c) and obtained 2-{3-[(2-chlorobenzenesulphonyl)-methylamino]-5-methylphenoxy}-N-pyridin-4-yl-acetamide as oil in 63% yield.

h) One reduced this compound as described in Example 1d) and obtained the title compound in 41% yield. M.p. 213 - 215°C.

Example 58

N-Methyl-N-{5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulphonamide hydrochloride

One hydrogenates the compound from Example 57 (0.86 g, 2 mmol) in 30 ml ethanol in the presence of 0.3 g 10% palladium on charcoal at room temperature and normal pressure. Hydrogen uptake 55 ml. One filtered and removed the solvent in a vacuum. One digested with ether and obtained 0.75 g (86%) of the title compound with the m.p. 182 - 184°C.

Example 59

N-{2-Methoxy-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulphonamide

a) To 8.5 g (50 mmol) 2-hydroxy-4-nitroanisole and 13.8 g (100 mmol) potassium carbonate in 120 ml acetonitrile one added dropwise in an ice bath 8.4 g (50 mmol) bromoacetic acid ethyl ester. One stirred for 12 h at room temperature, removed the solvent in a vacuum, mixed the residue with water and extracted with ethyl acetate. One dried the organic phase with sodium sulphate, filtered and removed the solvent in a vacuum. One obtained 12.7 g (quantitative) 2-(2-methoxy-5-nitrophenoxy)-acetic acid ethyl ester as oil. MS (m/e) = 255.

b) One hydrogenated this compound (12.1 g, 47 mmol) in 300 ml methanol in the presence of 5 g Raney nickel at normal pressure and room temperature. After 3.4 l hydrogen have been taken up, one filtered and removed the solvent in a vacuum. One obtained 10.7 g (quantitative) 2-(2-methoxy-5-aminophenoxy)-acetic acid ethyl ester as oil. MS (m/e) = 225.

c) One reacted this compound (10.7 g, 47 mmol) with benzenesulphonyl chloride as described in Example 1a) and obtained 17.2 g (quantitative) 2-(2-methoxy-

5-benzenesulphonylamino-phenoxy)-acetic acid ethyl ester. MS (m/e) = 413.

d) According to the instructions of Example 1b), one obtained 11.8 g (74%) 2-(2-methoxy-5-benzenesulphonylamino-phenoxy)-acetic acid from this compound. MS (m/e) = 337.

e) According to the instructions of Example 1c, one obtained 5 g (35%) N-(4-pyridinyl)-2-(2-methoxy-5-benzenesulphonylamino-phenoxy)-acetamide with the m.p. 179°C from this compound.

f) According to the instructions of Example 23, one obtained the title compound with the m.p. 188 - 189°C from this compound.

Example 60

N-{2-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulphonamide

was prepared analogously to Example 59 except that in step a) 2-hydroxy-4-nitrotoluene was used instead of 2-hydroxy-4-nitroanisole. One prepared this precursor as follows: one stirred 100 g 2-amino-4-nitrotoluene into 300 ml conc. sulphuric acid at 50°C until all was dissolved (30 min), added 2.5 kg ice thereto, cooled to -15°C and so added thereto dropwise a solution of 50 g sodium nitrite in 200 ml water that the temperature did not exceed 0°C. One added this solution to a mixture of 500 ml concentrated sulphuric acid and 1 l water which was boiling under reflux. One boiled for 1 hour under reflux, left to stand for 12 h and filtered off the precipitate with suction. One obtained 87.1 g (87%) 2-hydroxy-4-nitrotoluene with the m.p. 117 - 120°C.

a) 2-(2-Methyl-5-nitrophenoxy)-acetic acid ethyl ester as oil. MS (m/e) = 239.

b) 2-(2-Methyl-5-aminophenoxy)-acetic acid ethyl ester as oil. MS (m/e) = 209.

c) 2-(2-Methyl-5-benzenesulphonylaminophenoxy)-acetic acid ethyl ester. M.p. 78 - 83°C.

d) 2-(2-Methyl-5-benzenesulphonylaminophenoxy)-acetic acid. M.p. 157 - 160°C.

e) N-(4-Pyridinyl)-2-(2-methyl-5-benzenesulphonylamino-phenoxy)-acetamide with the m.p. 157 - 161°C.

f) Title compound with the m.p. 179 - 180°C.

Example 61

Benzenesulphonic acid 5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

a) One heated 7.1 g (50 mmol) 5-methylresorcinol, 10 g (100 mmol) potassium hydrogen carbonate and 12.6 g (55 mmol) bromoacetic acid benzyl ester in 70 ml acetonitrile for 24 hours under reflux. One removed the solvent in a vacuum, added water to the residue and extracted with ether, extracted the ether phase three times with 0.1 N sodium hydroxide solution, dried the ether phase over sodium sulphate, filtered and removed the solvent in a vacuum. One separated the residue (7.75 g) over silica gel with isohexane/ethyl acetate (9:1) and obtained 4.0 g (29%) 2-(3-hydroxy-5-methylphenoxy)-acetic acid benzyl ester as oil. MS (m/e) = 272.

b) One reacted 2.0 g (7.5 mmol) of this compound with benzenesulphonyl chloride analogously to Example 1a) and obtained 2.1 g (68%) 2-(3-benzenesulphonyloxy-5-methylphenoxy)-acetic acid benzyl ester as oil. MS (m/e) = 412.

c) One hydrogenated 2.0 g (5 mmol) of this compound in 150 ml methanol in the presence of 0.5 g 10% palladium on charcoal for 1 h at room temperature and normal pressure until 140 ml hydrogen had been taken up. One filtered, added ether thereto and extracted three times with sodium bicarbonate solution. One acidified the sodium bicarbonate

solution with 2 N sulphuric acid, extracted with ether, dried, removed the solvent in a vacuum and obtained 600 mg (38%) 2-(3-benzenesulphonyloxy-5-methylphenoxy)-acetic acid. MS (m/e) = 322.

d) One reacted 0.6 g (2 mmol) of this compound with 4-aminopyridine analogously to Example 1c) and obtained N-(pyridin-4-yl)-2-(3-benzenesulphonyloxy-5-methylphenoxy)-acetamide (16%). MS (m/e) = 392.

e) One obtained the title compound therefrom analogously to Example 23. M.p. 144 - 146°C.

Example 62

2-Chlorobenzenesulphonic acid 5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

was prepared analogously to Example 61. M.p. 156 - 158°C.

Intermediate steps: 2-[3-(2-chlorobenzenesulphonyloxy)-5-methylphenoxy]-acetic acid: m.p. 157 - 161°C.
N-(Pyridin-4-yl)-2-[3-(2-chlorobenzenesulphonyloxy)-5-methylphenoxy]-acetamide. MS (m/e) = 432.

Example 63

4-Fluorobenzenesulphonic acid 5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

was prepared analogously to Example 61 except that in step b) one used 4-fluorobenzenesulphonyl chloride. M.p. 161 - 163°C.

Example 64

1-Naphthalenesulphonic acid 5-methyl-3-[2-pyridin-4-ylamino)-ethoxy]-phenyl ester

was prepared analogously to Example 61 except that in step b) one used 1-naphthalenesulphonyl chloride. M.p. 95 - 99°C.

Example 65

2-Thiophenesulphonic acid 5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

a) One covered 24.8 g (200 mmol) 5-methylresorcinol, 43.8 g (240 mmol) 2-thiophenesulphonyl chloride and 1.5 g solid sodium bicarbonate in 200 ml water with 100 ml ether and maintained pH = 7.2 with a dosing apparatus with saturated sodium bicarbonate solution. One stirred for 12 h at room temperature at pH = 7.2, separated off the water phase, dried the ether phase with sodium sulphate, filtered and removed the solvent in a vacuum. One obtained thiophenesulphonic acid 3-hydroxy-5-methylphenyl ester in a quantitative yield as oil. MS (m/e) = 270..

b) One reacted this compound with bromoacetic acid ethyl ester analogously to Example 18a and obtained 2-[3-(2-thiophenesulphonyloxy)-5-methylphenoxy]-acetic acid ethyl ester. MS (m/e) = 356.

c) One obtained 2-[3-(-2-thiophenesulphonyloxy)-5-methylphenoxy]-acetic acid from this compound analogously to Example 1b) with the m.p. 142 - 143°C.

d) One obtained N-(pyridin-4-yl)-2-[3-(2-thiophene-sulphonyloxy)-5-methylphenoxy]-acetamide from this compound analogously to Example 1c). M.p. 136 - 138°C.

e) One obtained the title compound with the m.p. 176°C from this compound.

Example 66

(2-Benzyloxycarbonyl-benzenesulphonic acid) 5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

a) One reacted 5-methylresorcinol analogously to Example 61a) with bromoacetic acid ethyl ester and obtained 2-(3-hydroxy-5-methylphenoxy)-acetic acid ethyl ester as oil. MS (m/e) = 210.

b) Analogously to Example 61b), one obtained therefrom 2-[3-(2-benzyloxycarbonyl)-benzenesulphonyloxy-5-methylphenoxy]-acetic acid ethyl ester (MS (m/e) = 484) as oil by reaction with 2-benzyloxycarbonyl-benzenesulphonyl chloride.

c) One saponified this compound for 4 h at room temperature analogously to Example 1b) and obtained 63% 2-[3-(2-benzyloxycarbonylbenzenesulphonyloxy)-5-methylphenoxy]-acetic acid. MS (m/e) = 456.

d) One obtained therefrom N-(pyridin-4-yl)-2-[3-(2-benzyloxycarbonylbenzenesulphonyloxy)-5-methyl-phenoxy]-acetamide. MS (m/e) = 532.

e) One obtained the title compound therefrom analogously to Example 23. MS (m/e) = 518.

Example 67

(2-Carboxybenzenesulphonic acid) 5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

One hydrogenated 2.5 g (1 mmol) of the compound from Example 66 in 100 ml methanolic ammonia solution in the presence of 1 g 10% palladium on charcoal at normal pressure and room temperature. One filtered, removed the solvent in a vacuum, triturated the residue with isopropanol, filtered off with suction and recrystallised from ethanol. One obtained 0.4 g (14%) of the title compound with the m.p. 189°C.

Example 68

(2-Methylbenzenesulphonic acid) 5-methyl-3-[2-pyridin-4-ylamino)-ethoxy]-phenyl ester

was prepared analogously to Example 61. M.p. 152 - 154°C.

Precursor: N-(pyridin-4-yl)-2-[3-(2-methylbenzene-sulphonyloxy)-5-methylphenoxy]-acetamide. M.p. 158 - 160°C.

Example 69

(2-Methoxybenzenesulphonic acid) 5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

was prepared analogously to Example 61. M.p. 116 - 119°C.

Precursor: N-(pyridin-4-yl)-2-[3-(2-methoxybenzenesulphonyloxy)-5-methylphenoxy]-acetamide. M.p. 156 - 159°C.

Example 70

(2-Nitrobenzenesulphonic acid) 5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

was prepared analogously to Example 61. M.p. 137 - 140°C.

Precursor: N-(pyridin-4-yl)-2-[3-(2-nitrobenzenesulphonyloxy)-5-methylphenoxy]-acetamide. MS (m/e) = 453.

Example 71

(2-Aminobenzenesulphonic acid) 5-methyl-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

One hydrogenated 1.0 g (2.33 mmol) of the compound from Example 70 in 40 ml methanol in the presence of 1 g Raney nickel for 1.5 h at room temperature and normal pressure. One filtered, removed the solvent in a vacuum, mixed the residue with 25 ml tetrahydrofuran and 25 ml ether, extracted with 0.05 M sodium hydroxide solution, dried the organic phase, filtered and removed the solvent in a vacuum. One obtained 0.5 g (54%) of the title compound with the m.p. 168 - 171°C.

Example 72

2-Chlorobenzenesulphonic acid 5-methyl-3-[2-(N-methyl-pyridin-4-ylamino)-ethoxy]-phenyl ester

a) One obtained N-methyl-N-(pyridin-4-yl)-2-[3-(2-chlorobenzenesulphonyloxy)-5-methylphenoxy]-acetamide (MS (m/e) = 447 by reaction of 2-[3-(2-chlorobenzenesulphonyloxy)-5-methylphenoxy]-acetic acid with 4-methylaminopyridine according to Example 62.

b) One obtained the title compound with the m.p. 152 - 161°C therefrom analogously to Example 23.

Example 73

Benzenesulphonic acid 5-chloro-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

a) One stirred 98.8 g (0.57 mol) 5-chlororesorcinol dimethyl ether and 108 ml (1.14 mol) boron tribromide in 400 ml methylene chloride for 72 h at room temperature. One extracted with water, extracted the aqueous phase with n-butanol, removed most of the n-butanol in a vacuum and left to crystallise for 12 h at 4°C. One obtained 19.5 g (24%) 5-chlororesorcinol with the m.p. 70 - 71°C.

b) One covered 3.0 g (21 mmol) of this compound in 50ml water with 20 ml ether, added saturated sodium bicarbonate solution thereto to a pH = 5.2. One added thereto slowly 8.6 ml (21 mmol) benzenesulphonyl chloride with maintenance of the pH value, increased the pH to 7.0 and stirred for 48 h at room temperature while keeping the pH value constant. One extracted with ether, extracted the ether phase with 0.1 N sodium hydroxide solution, acidified the sodium hydroxide solution with 2 N sulphuric acid and extracted three times with ether. One removed the solvent in a vacuum and obtained 1.7 g (28%) benzenesulphonic acid 3-chloro-5-hydroxyphenyl ester. MS (m/e) = 284.

c) One reacted this compound with bromoacetic acid ethyl ester analogously to Example 18a) and obtained 2-[3-chloro-5-(phenylsulphonyloxy)-phenoxy]-acetic acid ethyl ester in 95% yield. MS (m/e) = 370.

d) One saponified this compound analogously to Example 1b) to obtain 2-[3-chloro-5-(phenylsulphonyloxy)-phenoxy]-acetic acid with the m.p. 136 - 138°C in 80% yield.

e) One reacted this compound with 4-aminopyridine analogously to Example 1c) and obtained N-(pyridin-4-yl)-2-[3-chloro-5-(phenylsulphinyloxy)-phenoxy]-acetamide with the m.p. 173 - 176°C in a 70% yield.

f) One reduced this compound analogously to Example 23 and obtained the title compound with the m.p. 144 - 146°C. Hydrochloride: m.p. 173 - 176°C.

Example 74

2-Chlorobenzenesulphonic acid 5-chloro-3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

was prepared analogously to Example 73. Intermediate steps:

b) 2-Chlorobenzenesulphonic acid 3-chloro-5-hydroxy-phenyl ester. M.p. 99 - 105°C.

c) 2-[3-Chloro-5-(2-chlorophenylsulphonyloxy)-phenoxy]-acetic acid ethyl ester as oil. MS (m/e) = 405.

d) 2-[3-Chloro-5-(2-chlorophenylsulphonyloxy)-phenoxy]-acetic acid. M.p. 140 - 142°C.

e) N-(Pyridin-4-yl)-2-[3-chloro-5-(2-chlorophenyl-sulphonyloxy)-phenoxy]-acetamide. M.p. 158 - 160°C.

f) Title compound. M.p. 149 - 150°C.

Example 75

Benzenesulphonic acid 3-[2-(pyridin-4-ylamino)-ethylamino]-phenyl ester

a) One hydrogenated 15 g (54 mmol) benzenesulphonic acid (3-nitrophenyl ester) in 200 ml methanol in the presence of 2.5 g 10% palladium on charcoal at normal pressure and room temperature. One filtered and removed the solvent in a vacuum. One heated the residue (13 g benzenesulphonic acid (3-amino-phenyl ester)), 4.3 g sodium acetate and 8.7 g bromoacetic acid ethyl ester in 10 ml ethanol to the boil for 12 h under reflux. One added water thereto and extracted with ether. One removed the ether in a vacuum and obtained 17.3 g (99%) 2-[3-(phenyl-sulphonyloxy)-phenylamino]-acetic acid ethyl ester as oil. MS (m/e) = 335.

b) One saponified this compound analogously to Example 1b) to give 2-[3-(phenylsulphonyloxy)-phenylamino]-acetic acid. Yield 65%. MS (m/e) = 307.

c) One reacted this compound with 4-aminopyridine analogously to Example 1c) to give N-(pyridin-4-yl)-2-[3-(phenylsulphonyloxy)-phenylamino]-acetamide. Oil. MS (m/e) = 383.

d) From this, one obtained the title compound analogously to Example 23. One dissolved 0.6 g of the compound obtained as an oil in 10 ml ethyl acetate and mixed with a solution of 220 mg cyclo-hexanesulphamic acid in 10 ml ethyl acetate. One added a few drops of isopropanol and left to crystallise. One obtained 0.3 g of the cyclaminate of the title compound with the m.p. 106 - 11°C.

Example 76

Benzenesulphonic acid 3-methyl-5-[2-(pyridin-4-ylamino)-ethylamino]-phenyl ester

a) One heated 12.3 g (100 mmol) 3-hydroxy-5-methyl-aniline (see Example 57) and 25.1 g (170 mmol) phthalic acid anhydride in 250 ml acetic acid to boil for 1 h under reflux. One added 250 ml water

thereto, filtered hot, added 250 ml water to the filtrate and left to crystallise. One filtered, dissolved the precipitate in 400 ml hot methanol, mixed with active charcoal, removed the water in a vacuum and obtained 21.7 g (86%) 3-phthalimido-5-methylphenol with the m.p. 170 - 175°C.

b) One obtained benzenesulphonic acid 3-methyl-5-phthalimidophenyl ester therefrom analogously to Example 1a). MS (m/e) = 393.

c) One stirred 3.9 g (10 mmol) of this compound and 0.7 ml (15 mmol) hydrazine hydrate in 10 ml ethanol and 30 ml methylene chloride for 12 h at room temperature, added 4 ml conc. hydrochloric acid thereto, stirred for 2 h at room temperature, filtered, removed the solvent in a vacuum, added 2 N sodium hydroxide solution to the residue and extracted with ether, washed the ether phase with water and saturated common salt solution, removed the ether in a vacuum and obtained 2.5 g (96%) benzenesulphonic acid 3-methyl-5-aminophenyl ester. MS (m/e) = 263.

d) One reacted 2.5 g (9.5 mmol) of this compound with tosyl chloride analogously to Example 1a) and obtained benzenesulphonic acid 3-methyl-5-(4-methyl-phenylsulphonylamino)-phenyl ester in quantitative yield. MS (m/e) = 417.

e) One alkylated this compound with bromoacetic acid ethyl ester analogously to Example 18a) and obtained 5 g (quantitative yield) [4-methylbenzenesulphonyl-(3-benzenesulphonyloxy-5-methylphenyl)-amino]-acetic acid ethyl ester. MS (m/e) = 503.

f) One heated 5 g (10 mmol) of this compound in 60 ml 6N hydrochloric acid to the boil for 6 h under reflux. One removed the solvent in a vacuum, added water thereto, neutralised with sodium hydrogen

carbonate, extracted with ethyl acetate, adjusted the aqueous phase to pH = 3 with 2 N hydrochloric acid and extracted with ethyl acetate. One removed the ethyl acetate in a vacuum and obtained 2 g (62%) (3-benzenesulphonyloxy-5-methylphenyl)-aminoacetic acid. MS (m/e) = 321.

g) One reacted this compound analogously to Example 1c) and obtained N-(pyridin-4-yl)-benzenesulphonyloxy-5-methylphenyl)-aminoacetamide in 12% yield. MS (m/e) = 397.

h) One obtained the title compound from this compound analogously to Example 23) as oil. MS (m/e) = 383.

Example 77

N-{3-[2-(Pyridin-4-ylamino)-ethylamino]-phenyl}-benzenesulphonamide

a) One heated 13.8 g (100 mmol) 3-nitroaniline, 12.3 g sodium acetate (150 mmol) and 25 g (150 mmol) bromoacetic acid ethyl ester in 5 ml dimethylsulphoxide for 48 h to 80°C. One poured on to 400 ml 0.5 N hydrochloric acid, added 15 ml isohexane and 10 ml ether thereto and left to crystallise. One filtered and obtained 18.7 g (84%) 3-nitrophenylaminoacetic acid ethyl ester. M.p. 92°C.

b) Analogously to Example 1b), one obtained therefrom 3-nitrophenylaminoacetic acid in 90% yield. M.p. 159 - 162°C.

c) Analogously to Example 1c), one obtained therefrom N-(pyridin-4-yl)-3-nitrophenylaminoacetamide in 89% yield. M.p. 196 - 198°C.

d) One hydrogenated 10.4 g (38 mmol) of this compound in 200 ml methanol and 100 ml ethyl acetate in the presence of 10 g Raney nickel at normal pressure and room temperature. One filtered, removed the solvent in a vacuum and obtained 7.7 g (82%) N-(pyridin-4-yl)-

(3-aminophenylamino)-acetamide. MS (m/e) = 292.

e) From this compound, analogously to Example 1a) one obtained N-(pyridin-4-yl)-(3-phenylsulphonyl-aminophenylamino)-acetamide in 68% yield. MS (m/e) = 382.

f) One obtained the title compound therefrom in 40% yield analogously to Example 23). MS (m/e) = 368.

Example 78

N-{3-[2-(Pyridin-4-ylamino)-ethylamino]-phenyl}-thiophene-2-sulphonamide

a) One obtained N-(pyridin-4-yl)-[3-(thiophene-2-yl-sulphonylamino)-phenylamino]-acetamide (MS (m/e) = 388) in 59% yield by reaction of the compound from Example 77d) with 2-thiophenesulphonyl chloride analogously to Example 1a).

b) One obtained the title compound therefrom analogously to Example 23) in 24% yield. M.p. 196 - 198°C.

Example 79

N-{3-[2-(Pyridin-4-ylamino)-ethylamino]-5-trifluoro-methylphenyl}-benzenesulphonamide

a) One added 15 g (270 mmol) iron powder portionwise to 24.5 g (100 mmol) 3,5-dinitrobenzenetrifluoride in 180 ml boiling glacial acetic acid. One poured on to water, extracted with ethyl acetate and neutralised the ethyl acetate phase with solid sodium bicarbonate. One filtered, removed the solvent in a vacuum, added the residue (26.3 g) to silica gel and eluted with isohexane/ethyl acetate (8:2). One obtained 13.0 g (63%) 3-nitro-5-trifluoromethylaniline with the m.p. 80 - 84°C.

b) One dissolved 5.0 g (24 mmol) of this compound in 20 ml sulphuric acid and 17 ml water, cooled to 0°C and added thereto a solution of 1.9 g (27 mmol)

sodium nitrite in 10 ml water. One added the cold solution to 250 ml boiling, concentrated copper sulphate solution. After ending of the nitrogen evolution, one extracted with ether. One extracted the ether phase with 0.05 N sodium hydroxide solution, acidified the aqueous phase with dilute sulphuric acid and extracted with ether. One removed the ether in a vacuum and obtained 3.4 g (68%) 3-nitro-5-trifluoromethylphenol with the m.p. 82 - 84°C.

C) One heated 36.7 g (600 mmol) ethanolamine and 80.7 g (550 mmol) phthalic acid anhydride in 290 ml toluene for 2 h under reflux on a water separator. After separation of 9.3 ml water, one left to cool, filtered and obtained 95.1 g (90%) N-(2-hydroxy-ethyl)-phthalimide with the m.p. 128 - 132°C.

d) One stirred 28.8 g (150 mmol) of this compound and 42.9 g (225 mmol) tosyl chloride in 200 ml pyridine for 3 h at room temperature, acidified with 2 N hydrochloric acid and extracted with ethyl acetate. One removed the ethyl acetate in a vacuum and obtained 48.3 g (85%) 4-toluenesulphonic acid (2-phthalimidoethyl) ester with the m.p. 144 - 148°C.

e) One stirred 1.7 g (12.5 mmol) of this compound, 2.6 g (12.5 mmol) of compound 79c) and 4.1 g potassium carbonate in 80 ml dimethylsulphoxide for 12 h at 50°C. One poured on to ice, extracted with ethyl acetate, washed the ethyl acetate with 0.01 N sodium hydroxide and saturated common salt solution, removed the ethyl acetate in a vacuum and obtained 1.9 g (40%) N-{2-[2-(3-nitro-5-trifluoromethyl-phenoxy)-ethyl]}-phthalimide with the m.p. 146 - 148°C.

f) One obtained 2-(3-nitro-5-trifluoromethylphenoxy)-ethylamine quantitatively therefrom analogously to Example 76c). MS (m/e) = 250.

g) One stirred 1.0 g (4 mmol) of this compound, 1.15 g (4.4 mmol) 4-nitrotetrachloropyridine (M. Roberts, H. Suschitzky, J. Chem. Soc. C 1968, 2844-2848) and 0.48 ml (4.4 mmol) N-methylmorpholine in 20 ml dioxane for 3 h at room temperature. One added water thereto, extracted with ethyl acetate, washed the ethyl acetate with water and saturated common salt solution, removed the ethyl acetate in a vacuum and obtained 1.4 g (75%) N-(tetrachloropyridin-4-yl)-2-(3-nitro-5-trifluoromethylphenoxy)-ethylamine with the m.p. 126 - 129°C.

h) One reduced this compound analogously to step a) and obtained N-(tetrachloropyridin-4-yl)-2-(3-amino-5-trifluoromethylphenoxy)-ethylamine with the m.p. 144 - 146°C.

i) One stirred 0.4 g (0.92 mmol) of this compound and 0.12 ml (0.92 mmol) benzenesulphonyl chloride in 5 ml pyridine for 3 h at room temperature, acidified with 2 N hydrochloric acid, extracted with ethyl acetate, washed with saturated common salt solution, removed the ethyl acetate in a vacuum and obtained 0.4 g (N-{3-[2-(tetrachloropyridin-4-ylamino)-ethoxy]-5-trifluoromethylphenyl}-benzenesulphonamide with the m.p. 139 - 143°C.

j) One hydrogenated 0.4 g (0.7 mmol) of this compound in 50 ml methanol in the presence of 3.5 mmol sodium methylate and 0.5 g 10% palladium on charcoal at room temperature and normal pressure. One filtered, added water thereto and extracted with ethyl acetate. One removed the ethyl acetate in a vacuum and obtained 0.2 g of the title compound with the m.p. 140 - 144°C.

Example 80

3-Methoxy-N-methyl-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzenesulphonamide

a) One stirred 92 g (0.4 mmol) 3,5-dinitrobenzoyl chloride and 28.4 g (0.44 mol) sodium azide in 240 ml glacial acetic acid for 8 h at room temperature, added 400 ml water thereto, filtered the precipitate and obtained 80.8 g (85%) 3,5-dinitrobenzoyl azide with the m.p. 105°C (decomp.).

b) One heated 80.8 g (0.34 mol) of this compound in 500 ml acetic acid anhydride carefully until gas evolution started (90 - 100°C) and kept at this temperature for 4 h. One removed the solvent in a vacuum, digested the residue with water and obtained 136 g (quantitative) N-(3,5-dinitrophenyl)-acetamide, m.p. 163°C.

c) One heated 136 g (0.34 mol) of this compound to the boil for 3 h under reflux in 500 ml ethanol and 500 ml concentrated hydrochloric acid, filtered off undissolved material, poured the filtrate into 2 l water and filtered off the yellow precipitate with suction and obtained 41.4 g (66%) 3,5-dinitroaniline. M.p. 140°C (decomp.).

d) One disolved 25 g (137 mmol) of this compound in 50 ml glacial acetic acid and 100 ml concentrated hydrochloric acid, added dropwise at -5°C 10.4 g (155 mmol) sodium nitrite in 20 ml water within 5 min, further stirred for 15 min at this temperature, cooled the brown suspension to -20°C and added it within 15 minutes to a solution of 2.7 g copper dichloride dihydrate in 200 ml glacial acetic acid saturated with sulphur dioxide and cooled to 0°C. One extracted with ethyl acetate, removed the ethyl acetate in a vacuum and dried at 10^{-2} torr. One obtained 35.4 g (97%) dinitrobenzenesulphonyl

chloride as brown solid which was used without further purification.

e) One obtained 4.9 g (39%) N-methyl-N-phenyl-3,5-dinitrobenzenesulphonamide with the m.p. 175 - 178°C analogously to Example 79i), from 10.2 g (38.2 mmol) of this compound and 4.5 ml (42 mmol) N-methylaniline.

f) One heated 3.5 g (10.4 mmol) of this compound in 31 ml 0.4 molar methanolic sodium methylate solution to the boil for 1 h under reflux. One removed the solvent in a vacuum, digested the residue with ethyl acetate and purified over a silica gel column (100 g silica gel). One eluted with isohexane/ethyl acetate 2:1 and obtained 2.5 g (75%) N-methyl-N-phenyl-3-methoxy-5-nitrobenzene-sulphonamide. M.p. 112°C.

g) One hydrogenated this compound analogously to Example 58 and obtained 2.3 g N-methyl-N-phenyl-3-methoxy-5-aminobenzenesulphonamide as oil. Ms (m/e) = 292.

h) One added dropwise a solution of 630 mg (9 mmol) sodium nitrite in 2 ml water to a suspension, cooled to 0°C, of 2.3 g (7.8 mmol) of this compound in 10 ml water and 5 ml concentrated sulphuric acid, stirred for 2 h at this temperature, decomposed with urea, heated for 15 min to 110°C, extracted with ethyl acetate, washed the ethyl acetate with 2 N sodium hydroxide solution, removed the solvent in a vacuum and obtained 300 mg (13%) N-methyl-N-phenyl-3-methoxy-5-hydroxybenzenesulphonamide as oil. MS (m/e) = 293.

i) One alkylated 250 mg (0.85 mmol) of this compound with 0.14 ml bromoacetic acid ethyl ester analogously to Example 18a) and obtained 360 mg (quant.) [3-methoxy-5-(methylphenylsulphamoyl)-phenoxy]-acetic acid ethyl ester as oil. MS (m/e) = 379.

j) One saponified this compound analogously to Example 1b) and obtained 300 mg [3-methoxy-5-(methylphenylsulphamoyl)-phenoxy]-acetic acid as viscous mass. MS (m/e) = 351.

k) From this compound, one obtained, analogously to Example 1a), 120 mg (33%) N-(pyridin-4-yl)-[3-methoxy-5-(methylphenylsulphamoyl)-phenoxy]-acetamide. M.p. 105°C.

l) From this compound, one obtained analogously to Example 1d) 45 mg (46%) of the title compound. MS (m/e) = 413.

Example 81

3-Methoxy-N-benzyl-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzenesulphonamide

a) From compound 80c) and N-benzylaniline, in a 65% yield, analogously to Example 80d), oneobtained N-benzyl-N-phenyl-3,5-dinitrobenzenesulphonamide. M.p. 200°C.

b) Analogously to Example 80c), one obtained therefrom in quant. yield N-benzyl-N-phenyl-3-methoxy-5-nitrobenzenesulphonamide. M.p. 142°C.

c) Analogously to 79a), one obtained therefrom in 56% yield N-benzyl-N-phenyl-3-methoxy-5-aminobenzenesulphonamide as viscous mass. MS (m/e) = 368.

d) Analogously to Example 80g), oneobtained therefrom N-benzyl-N-phenyl-3-methoxy-5-hydroxybenzenesulphonamide. MS (m/e) = 369.

e) Analogously to Example 18a), one obtained therefrom [3-methoxy-5-(benzylphenylsulphamoyl)-phenoxy]-acetic acid ethyl ester in 30% yield. MS (m/e) = 455

f) Analogously to Example 1b), one obtained quantitatively therefrom [3-methoxy-5-(methylphenyl-

sulphamoyl)-phenoxy]-acetic acid. MS (m/e) = 427.

g) Analogously to Example 1c), one obtained N-(pyridin-4-yl)-[3-methoxy-5-(methylphenylsulphamoyl)-phenoxy]-acetamide in 42% yield. M.p. 175°C.

h) Analogously to Example 1d), one obtained the title compound therefrom in 50% yield as amorphous powder. MS (m/e) = 489.

Example 82

3-Methoxy-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzenesulphonamide

One hydrogenated 60 mg (0.12 mmol) of the compound Example 81) analogously to Example 58) and obtained 20 mg (40%) of the title compound as amorphous powder. MS (m/e) = 399.

Example 83

N-Methyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-5-methoxy-phenyl}-benzenesulphonamide

a) One reacted 18.3 g (100 mmol) of the compound 80c) with 14.3 g (110 mmol) benzenesulphonyl chloride analogously to Example 79i) and obtained 32.5 g (quant.) N-(3,5-dinitrophenyl)-benzenesulphonamide. M.p. 165°C.

b) One methylated 44 g (136 mmol) of this compound analogously to Example 12a) and obtained 25.1 g (54%) N-methyl-N-(3,5-dinitrophenyl)-benzene-sulphonamide. M.p. 125°C.

c) One reduced 6.8 g (20 mmol) of this compound analogously to 79a) and obtained 6.1 g (quant.) N-methyl-N-(3-amino-5-nitrophenyl)-benzenesulphon-amide as amorphous powder. MS (m/e) = 307.

d) From 6.1 g (20 mmol) of this compound, one obtained analogously to Example 80g) 1.8 g (30%) N-methyl-N-

(3-hydroxy-5-nitrophenyl)-benzenesulphonamide as amorphous powder. MS (m/e) = 308. (380 after silylation).

e) One stirred 1.2 g (4 mmol) of this compound, 6 ml 1 N sodium hydroxide solution, 1.3 g tetrabutylammonium bromide, 6 ml dichloromethane and 0.4 ml iodomethane for 12 h at room temperature. One separated off the organic phase, removed the solvent in a vacuum and purified the residue on silica gel (150 g). One eluted with isohexane/ethyl acetate = 2:1 and obtained 240 mg (18%) N-methyl-N-(3-methoxy-5-nitrophenyl)-benzenesulphonamide. M.p. 136°C.

f) One hydrogenated this compound analogously to Example 58 and obtained N-methyl-N-(3-methoxy-5-aminophenyl)-benzenesulphonamide quantitatively as amorphous powder. MS (m/e) = 292.

g) Analogously to Example 80g), one obtained therefrom N-methyl-N-(3-methoxy-5-hydroxyphenyl)-benzenesulphonamide in 74% yield as amorphous powder. MS (m/e) = 293.

h) Analogously to Example 18a), one obtained therefrom [3-methoxy-5-(N-methylphenylsulphonylamino)-phenoxy]-acetic acid ethyl ester in 89% yield as amorphous powder. MS (m/e) = 379.

i) Analogously to Examples 81f) to 81h), one obtained therefrom [3-methoxy-5-(N-methylphenylsulphonylamino)-phenoxy]-acetic acid (74%; MS = 351), N-(pyridin-4-yl)-[3-methoxy-5-(N-methylphenylsulphonylamino)-phenoxy]-acetamide (34%; MS = 427) and the title compound as amorphous powder (MS (m/e) = 413.

Example 84

3-Chloro-N-methyl-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzenesulphonamide

a) One reduced the compound 80e) analogously to Example 79a) and obtained N-methyl-N-phenyl-3-amino-5-nitrobenzenesulphonamide in 50% yield. M.p. 175°C.

b) One added dropwise a solution of 760 mg (11 mmol) sodium nitrite in 2 ml water to 3.5 g (10 mmol) of this compound in 40 ml 6 N hydrochloric acid at 0°C and then poured the suspension obtained into a solution which one had prepared as follows: one dissolved 3.75 g copper sulphate pentahydrate and 1.35 g common salt in 12 ml warm water, added dropwise thereto a solution of 950 mg (7.5 mmol) sodium sulphite in 3 ml water, quickly filtered off the precipitate and dissolved it in 6 ml concentrated hydrochloric acid. One slowly heated to 100°C, cooled, extracted with ethyl acetate and filtered over a silicic acid gel (100 g silica gel). One eluted with isohexane/ethyl acetate and obtained 1.45 g (43%) N-methyl-N-phenyl-3-chloro-5-nitrobenzenesulphonamide. M.p. 143°C.

c) One reduced this compound quantitatively analogously to Example 79a) to give N-methyl-N-phenyl-3-chloro-5-aminobenzenesulphonamide. Amorphous powder. MS (m/e) = 296.

d) From this, analogously to Examples 83g) to 83i), one prepared N-methyl-N-phenyl-3-chloro-5-hydroxybenzenesulphonamide (69%, amorphous, MS = 297); [3-chloro-5-(methylphenylsulphamoyl)-phenoxy]-acetic acid ethyl ester (92%, amorphous, MS = 383); [3-chloro-5-(methylphenylsulphamoyl)-phenoxy|-acetic acid (quant., amorphous, MS = 355); N-(pyridin-4-yl)-[3-chloro-5-(methylphenylsulphamoyl)-phenoxy]-acetamide (32%, amorphous, MS = 431); title compound (40%; amorphous MS = 417).

Example 85

3-Chloro-N-benzyl-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzenesulphonamide

a) One reacts 12.3 g (45 mmol) of compound 80d) with 9.2 g (50 mmol) benzylamine analogously to Example 79i) and obtained 31.3 g (83%) N-benzyl-N-phenyl-3,5-dinitrobenzenesulphonamide. M.p. 205°C.

b) One reduces this compound analogously to Example 79a) and obtains N-benzyl-N-phenyl-3-amino-5-nitro-benzenesulphonamide quantitatively. M.p. 170°C.

c) One obtains therefrom N-benzyl-N-phenyl-3-chloro-5-nitrobenzenesulphonamide in 37% yield analogously to Example 84b). M.p. 160°C.

d) One prepares the following compounds analogously to Examples 84c) to 84d): N-benzyl-N-phenyl-3-chloro-5-aminobenzenesulphonamide (quant., amorphous, MS = 372); N-benzyl-N-phenyl-3-chloro-5-hydroxybenzene-sulphonamide (quant., amorphous, MS = 373); [3-chloro-5-(benzylphenylsulphamoyl)-phenoxy]-acetic acid ethyl ester (15%, oil, MS = 459; [3-chloro-5-(benzylphenylsulphamoyl)-phenoxy]-acetic acid (50% amorphous, MS = 431); N-(pyridin-4-yl)-[3-chloro-5-(benzylphenylsulphamoyl)-phenoxy]-acetamide (44%, amorphous, MS = 507); title compound (40%, amorphous, MS = 493).

Example 86

3-Chloro-N-benzyl-N-phenyl-5-[2-(pyridin-4-ylamino)-ethylamino]-benzenesulphonamide

One prepared the following compounds from N-benzyl-N-phenyl-3-chloro-5-aminobenzenesulphonamide (Example 85d) analogously to Examples 83h) to 83i): [3-chloro-5-(benzylphenylsulphamoyl)-phenylamino]-acetic acid ethyl ester (18%, oil, MS = 458); [3-chloro-5-(benzylphenylsulphamoyl)-phenylamino]-acetic

acid (quant., amorphous, MS = 439); N-(pyridin-4-yl)-[3-chloro-5-(benzylphenylsulphamoyl)-phenylamino]-acetamide (25%, amorphous, MS = 506); title compound (50%, amorphous, MS = 492).

Example 87

N-Methyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulphonamide

a) One reacted N-methyl-N-(3-amino-5-nitrophenyl)-benzenesulphonamide (Example 83c) analogously to Example 84b) to give N-methyl-N-(3-chloro-5-nitrophenyl)-benzenesulphonamide (52%, amorphous, MS (m/e) = 326).

b) One reduced this compound analogously to Example 79a) to give N-methyl-N-(3-chloro-5-aminophenyl)-benzenesulphonamide (42%, oil, MS = 296); [3-chloro-5-(N-methylphenylsulphonylamino)-phenoxy]-acetic acid ethyl ester (89%, amorphous, MS (m/e) = 383); [3-chloro-5-(N-methylphenylsulphonylamino)-phenoxy]-acetic acid (88%; MS = 355); N-(pyridin-4-yl)-[3-chloro-5-(N-methylphenylsulphonylamino)-phenoxy]-acetamide (28%; MS = 431) and the title compound (56%) as amorphous powder. MS (m/e) = 417.

Example 88

N-Benzyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-5-chloro-phenyl}-benzenesulphonamide

a) One benzylated the compound of Example 83a) with benzyl bromide analogously to Example 92c) and obtained N-benzyl-N-(3,5-dinitrophenyl)-benzene-sulphonamide (quant.). M.p. 170°C.

b) One reduced this compound analogously to 79a) and obtained 27% N-benzyl-N-(3-amino-5-nitrophenyl)-benzenesulphonamide as amorphous powder. MS (m/e) = 383.

c) One obtained N-benzyl-N-(3-chloro-5-nitrophenyl)-benzenesulphonamide from this compound analogously to Example 84b) in a 45% yield. M.p. 148°C.

d) One reduced this compound analogously to Example 79a) and obtained 34% N-benzyl-N-(3-chloro-5-aminophenyl)-benzenesulphonamide. M.p. 145°C.

e) One obtained the following compounds therefrom analogously to Examples 83g) to 83i): N-benzyl-N-(3-chloro-5-hydroxyphenyl)-benzenesulphonamide (quant., amorphous, MS (m/e) = 373); [3-chloro-5-(N-benzylphenylsulphonylamino)-phenoxy]-acetic acid ethyl ester (quant., amorphous, MS (m/e) = 459); [3-chloro-5-(N-benzylphenylsulphonylamino)-phenoxy]-acetic acid (82%, m.p. 180°C (decomp.)); N-(pyridin-4-yl)-[3-chloro-5-(N-benzylphenylsulphonylamino)-phenoxy]-acetamide (54%; m.p. 178°C) and the title compound as amorphous powder. MS (m/e) = 493.

Example 89

N-{3-[2-Pyridin-4-ylamino)-ethylamino]-5-bromophenyl}-benzenesulphonamide

a) One added dropwise a solution of 7.6 g (110 mmol) sodium nitrite in 15 ml water within 15 min to 18.3 g (100 mmol) 3,5-dinitroaniline (Example 80c) in 100 ml glacial acetic acid and 100 ml 47% aqueous hydrobromic acid at 0°C and proceeded further as described in Example 84b). One obtained 21.7 g (88%) 3,5-dinitrobromobenzene. M.p. 65°C.

b) One reduced this compound analogously to Example 79a) and obtained 17.4 g (91%) 3-bromo-5-nitroaniline. M.p. 105°C.

c) One alkylated this compound analogously to Example 18a) and obtained 3-bromo-5-nitrophenylaminoacetic acid ethyl ester quantitatively. Amorphous. MS (m/e) = 303.

d) One saponified this compound analogously to Example 1b) and obtained bromo-5-nitrophenylamino acetic acid (22%, amorphous, MS (m/e) = 274.

e) One reacted this compound analogously to Example 1c) and obtained N-(pyridin-4-yl)-(3-bromo-5-nitrophenylamino)-acetamide in 29% yield. M.p. 240°C.

f) One hydrogenated this compound analogously to Example 58) and obtained N-(pyridin-4-yl)-(3-bromo-5-aminophenylamino)-acetamide quantitatively. Amorphous. MS (m/e) = 321.

g) Analogously to Example 79i, one obtained therefrom N-(pyridin-4-yl)-[3-bromo-5-benzenesulphonylamino-phenylamino)-acetamide. Amorphous. MS (m/e) = 460.

h) One obtained the title compound therefrom analogously to Example 1d). Amorphous. MS (m/e) = 446.

Example 90

Benzenesulphonic acid 3-ethyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl ester

a) One heated 20 g 3,5-dimethoxybenzoic acid (110 mmol) in 80 ml thionyl chloride to the boil for 1 h under reflux. One removed the solvent in a vacuum, took up the residue in 500 ml dry methylene chloride and passed dry ammonia for 90 min over the ice-cooled solution. One stirred for a further 2 h at room temperature, removed the solvent in a vacuum, stirred the residue for 12 h in 200 ml water and 50 ml saturated sodium hydrogen carbonate solution, filtered, dissolved the precipitate in ethyl acetate, filtered over active charcoal and removed the ethyl acetate up to commencement of crystallisation. One obtained 10.8 g 3,5-dimethoxybenzamide. M.p. 145°C.

b) One added dropwise 19.5 ml (310 mmol) iodomethane in 30 ml ether to 7.6 g (310 mmol) magnesium in 10 ml dry ether, heated to the boil for 30 min under reflux and then added 11.6 g (63 mmol) 3,5-dimethoxybenzamide portionwise. One heated to the boil for 22 h under reflux, added 125 ml 6 N hydrochloric acid dropwise thereto with ice cooling, stirred for 16 h at room temperature, washed the organic phase with water, removed the solvent in a vacuum and obtained 9.4 g 3,5-dimethoxyacetophenone as oil. MS (m/e) = 180.

c) One hydrogenated 9.4 g (52 mmol) of this compound in 150 ml ethanol and 2 ml concentrated hydrochloric acid in the presence of 1 g palladium at 50°C and 5 bar pressure. One filtered, removed the solvent in a vacuum and obtained 6.8 g (78%) 3,5-dimethoxy-ethylbenzene as oil. MS (m/e) = 166.

d) One heated 6.8 g (41 mmol) of this compound in 65 ml glacial acetic acid and 25 ml concentrated 47% hydrobromic acid to the boil for 4 h under reflux. One removed the solvent in a vacuum, added water to the residue, extracted with ethyl acetate, washed the ethyl acetate with water, removed the solvent in a vacuum and filtered the residue over silica gel (isohexane/ethyl acetate = 3:1). One obtained 3.9 g (69%) 5-ethylresorcinol as oil. MS (m/e) = 138.

e) One stirred 3.9 g (28 mmol) of this compound and 4.3 ml (33 mmol) benzenesulphonyl chloride in 30 ml ether and 60 ml saturated sodium hydrogen carbonate solution for 48 h at room temperature. One separated off the ether phase, removed the solvent in a vacuum, filtered the residue over silica gel (isohexane/ethyl acetate 3:1) and obtained 5.4 g (69%) benzene-sulphonic acid 3-hydroxy-5-ethylphenyl ester as oil. MS (m/e) = 278.

f) One obtained the following compounds analogously to Examples 81e) to 81h): (3-benzenesulphonyloxy-5-ethylphenyloxy)-acetic acid ethyl ester (77%, oil, MS (m/e) = 364); (3-benzenesulphonyloxy-5-ethylphenyloxy)-acetic acid (59%, amorphous, MS (m/e) = 336); N-(pyridin-4-yl)-(3-benzenesulphonyloxy-5-ethylphenyloxy)-acetamide (70%, amorphous, MS (m/e) = 412); title compound (10%, m.p. 136°C).

Example 91

N-Benzyl-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-5-methylphenyl}-benzenesulphonamide

a) One reacted 107 g (1 mol) para-toluidine with p-tosyl chloride analogously to Example 79i) and obtained 280 g (quant.) N-(4-methylphenyl)-4-methylbenzenesulphonamide as oil which one reacted without further purification. Crystals from ether with m.p. 105°C.

b) One introduced 21 g (80 mmol) of this compound into 56 ml fuming nitric acid with ice cooling, then slowly added dropwise 32 ml concentrated sulphuric acid, poured on to ice, washed the precipitate with water and obtained 46.6 g (73%) yellow solid with m.p. 170°C, one heated for 10 min to 100°C in 80 ml concentrated sulphuric acid, poured on to ice water and extracted with ethyl acetate. One removed the solvent in a vacuum and obtained 20 g (88%) 2,6-dinitro-4-methylaniline with the m.p. 171°C.

c) One added 800 ml glacial acetic acid to 20.5 g (300 mmol) sodium nitrite in 220 ml sulphuric acid and 53.5 g (270 mmol) 2,6-dinitro-4-methylaniline portionwise, one stirred for 3 h at 40°C until all had dissolved and added this solution dropwise to an ice-cooled suspension of 20 g copper oxide in ethanol, removed the solvent in a vacuum, added water thereto and extracted with ethyl acetate. One

carried out this preparation again for a second time and obtained a total of 88 g (88%) 3,5-dinitrotoluene as amorphous powder.

d) One saturated 88 g (480 mmol) of this compound in 520 ml methanol with 53 g ammonia and then passed in hydrogen sulphide for 15 min, whereby the temperature increased to 52°C. One boiled for 30 min under reflux, poured on to 1 l water and obtained 60.5 g (82%) 3-methyl-5-nitroaniline. M.p. 97°C.

e) One obtained N-(3-methyl-5-nitrophenyl)-benzene-sulphonamide (quantitative) therefrom analogously to Example 79i). M.p. 165°C.

f) Analogously to Examples 88a) to 88b), one obtained therefrom N-benzyl-N-(3-methyl-5-nitrophenyl)-benzenesulphonamide (83%) m.p. 154°C and N-benzyl-N-(3-methyl-5-aminophenyl)-benzenesulphonamide (34%), amorphous, MS (m/e) = 352.

g) Analogously to Examples 81c) to 81h), one obtained the following compounds therefrom: [3-(benzene-sulphonylbenzylamino)-5-methylphenylamino]-acetic acid ethyl ester (quant., oil, MS (m/e) = 438); [3-(benzenesulphonylbenzylamino)-5-methylphenyl-amino]-acetic acid (90%, amorphous, MS (m/e) = 410); N-(pyridin-4-yl)-[3-(benzenesulphonylbenzylamino)-5-methylphenylamino]-acetamide (10%, amorphous, MS (m/e) = 486); title compound (47%, amorphous, MS (m/e) = 472).

Example 92

(Benzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetic acid ethyl ester

a) One stirred 100 g 4-nitrotetrachloropyridine and 50.6 ml ethanolamine in 1.2 l dioxane for 90 min at room temperature, removed the solvent in a

vacuum, added water to the residue, extracted with ethyl acetate, washed the ethyl acetate with water, removed the solvent in a vacuum and obtained 105 g (72%) 4-(2-hydroxyethylamino)-tetrachloropyridine. M.p. 131 - 133°C.

b) One stirred 36.3 g (130 mmol) of this compound and 12.1 ml (170 mmol) acetyl chloride in 450 ml glacial acetic acid for 12 h at room temperature, poured on to ice, neutralised with concentrated ammonia, extracted with ethyl acetate, washed the ethyl acetate with water, removed the solvent in a vacuum and obtained 41.6 g (99%) acetic acid 2-(tetrachloropyridin-4-ylamino)-ethyl ester. M.p. 72 - 75°C.

c) One added a suspension of 10.8 g sodium hydride in 150 ml dimethylformamide to 109 g (340 mmol) of this compound in 700 ml dry dimethylformamide and subsequently added dropwise thereto a solution of 54 ml benzyl bromide in 350 ml dimethylformamide at 10°C. One stirred for 2 h at room temperature, poured on to 7 l ice water, filtered, washed the precipitate with water, dissolved it in 800 ml methanol and 200 ml dichloromethane, concentrated until crystallisation began and left to crystallise. One obtained 120 g acetic acid 2-(benzyltetrachloropyridin-4-ylamino)-ethyl ester. M.p. 97 - 100°C.

d) One added enough dimethylformamide to 108 g (260 mmol) of this compound in 1.2 l ethanol and 390 ml 2 N sodium hydroxide solution until all had dissolved (ca. 0.5 l). One stirred for 12 h at room temperature, removed the solvent in a vacuum (finally at 10^{-2} torr), added 3 l water to the residue and extracted with 1 l ethyl acetate, washed the ethyl acetate with 3 l water, removed the solvent in a vacuum and obtained 99 g (quant.) N-benzyl-N-(2-hydroxyethyl)-N-(tetrachloropyridin-4-yl)-amino as oil. MS (m/e) = 366.

e) One added 73 ml (520 mmol) triethylamine to 107 g (290 mmol) of this compound in 800 ml dichloromethane, cooled to 0°C and added dropwise thereto a solution of 67.1 g (350 mmol) 4-toluenesulphonyl chloride in 500 ml dichloromethane. One kept the solution for 16 h at 4°C, added water thereto, separated off the organic phase and removed the solvent in a vacuum. One obtained 90.6 g (64%) 4-toluenesulphonic acid 2-(benzyltetrachloropyridin-4-ylamino)-ethyl ester. M.p. 114 - 116°C.

f) One stirred 57.2 g (240 mmol) of this compound, 64.8 g (260 mmol) 3-phthalimido-5-methylphenol (Example 76a) and 66.2 g (480 mmol) potassium carbonate in 1.15 l dimethylsulphoxide for 72 h at room temperature, poured on to 3 l water, filtered, digested the residue with diisopropyl ether and obtained 63 g (38%) N-benzyl-N-(tetrachloropyridin-4-yl)-N-[2-(3-phthalimido-5-methylphenoxy)-ethyl]-amine. M.p. 142 - 144°C.

g) One stirred 19.1 g (31.8 mmol) of this compound, 2.3 ml (47.6 mmol) hydrazine hydrate and 50 ml ethanol in 100 ml dichloromethane for 12 h at room temperature, removed the solvent in a vacuum, suspended the residue in 150 ml 2 N sodium hydroxide solution, extracted with dichloromethane, washed the organic phase with water, removed the solvent in a vacuum, digested the residue with methanol and obtained 11.5 g (77%) N-benzyl-N-(tetrachloropyridin-4-yl)-N-[2-(3-amino-5-methylphenoxy)-ethyl]-amine. M.p. 91 - 93°C.

h) One reacted 11.5 g (25.5 mmol) of this compound analogously to Example 79i) with 3.51 ml (27.0 mmol) benzenesulphonyl chloride and obtained 13.7 g (91%) N-{3-[2-(benzyltetrachloropyridin-4-ylamino)-ethoxy]-5-methylphenyl}-benzenesulphonamide. M.p. 147 - 149°C.

1) One added 3.0 g (4.00 mmol) of this compound in 15 ml dry dimethylformamide to 147 mg (6.38 mmol) sodium hydride in 2 ml dimethylformamide and then added 0.6 ml (5.4 mmol) bromoacetic acid ethyl ester dropwise thereto. One poured on to 300 ml water, extracted with ethyl acetate, washed the organic phase with water, removed the solvent in a vacuum and obtained 3.15 g (91%) (benzenesulphonyl-{3-methyl-5-[2-(benzyltetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetic acid ethyl ester. M.p. 141 - 142°C.

j) One stirred 3.15 g (4.5 mmol) of this compound, 50 ml trifluoroacetic acid and 6.8 ml 1,2,3-trimethylbenzene for 12 h at room temperature, poured on to ice water, neutralised with concentrated ammonia, extracted with ether, washed the ether phase with water, removed the solvent in a vacuum, filtered the residue over silica gel (ethyl acetate/isohexane 1:2.5) and obtained 2.50 g (91%) (benzene-sulphonyl-{3-methyl-5-[2-(tetrachloropyridin-4-yl-amino)-ethoxy]-phenyl}-amino)-acetic acid ethyl ester as oil. MS (m/e) = 605.

k) One hydrogenated 3.5 g (5.76 mmol) of this compound and 4.0 g potassium carbonate in 40 ml tetrahydro-furan and 40 ml methanol in the presence of 1.0 g 10% palladium on charcoal at 4 bar pressure. One filtered after 48 h, removed the solvent in a vacuum, filtered over silica gel (methylene chloride/methanol = 4:1) and obtained 2.1 g (78%) of the title compound. Amorphous. MS (m/e) = 469.

Example 93

(Benzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetic acid

One saponifies 1.20 g (2.55 mmol) of the compound of Example 92) in 20 ml ethanol with 5.1 ml 1 N sodium

hydroxide solution for 2 h at 45°C. One neutralised with 1 N hydrochloric acid, removed the solvent in a vacuum, took up the residue in 20 ml water and left to crystallise. One obtained 0.97 g (86%) of the title compound. M.p. 100 - 102°C (decomp.).

Example 94

(Benzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

One dissolved 1.5 g (3.2 mmol) of the compound of Example 92) in 12 ml concentrated ammonia and 30 ml methanol. After 12 h at room temperature,one filtered and obtained 0.99 g (70%) of the title compound. M.p. 163 - 165°C.

Example 95

N-(2-Hydroxyethyl)-(benzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in 60% yield analogously to Example 94 with ethanolamine instead of ammonia. M.p. 169 - 170°C.

Example 96

N-(3-Hydroxyethyl)-(benzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in 70% yield analogously to Example 94 with 3-propanolamine instead of ammonia. M.p. 148 - 152°C.

Example 97

N-Methyl-(benzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in 53% yield analogously to Example 94 with 25% ethanolic methylamine solution instead of ammonia. M.p. 136 - 140°C.

Example 98

N,N-Dimethyl-(benzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in 38% yield analogously to Example 94 with 41% ethanolic dimethylamine solution instead of ammonia. Amorphous. MS (m/e) = 468.

Example 99

N-(2-Aminoethyl)-(benzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in 45% yield analogously to Example 94 with ethylenediamine instead of ammonia. Amorphous. MS (m/e) = 483.

Example 100

N-(2-Aminoethyl)-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-5-methylphenyl}-amino)-benzenesulphonamide

One reduced the compound of Example 94) analogously to Example 18c) and obtained the title compound in 34% yield. Amorphous MS (m/e) = 426.

Example 101

N-(2,3-Dihydroxypropyl)-(benzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in 40% yield analogously to Example 94 with 2,3-dihydroxypropylamine instead of ammonia. M.p. 148 - 151°C.

Example 102

N-(2,3-Dihydroxypropyl)-N-{3-[2-(pyridin-4-ylamino)-ethoxy]-5-methylphenyl}-benzenesulphonamide

a) One stirred 10.0 g (75.7 mmol) 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane and 14.3 g (75 mmol) 4-toluenesulphonic acid chloride in 7 ml pyridine for 16 h at room temperature, poured on to 200 ml water, extracted with ethyl acetate and removed the solvent in a vacuum. One recrystallised from isohexane and obtained 10.3 g (48%) 4-methylbenzene-sulphonic acid (2,2-dimethyl-1,3-dioxolan-4-yl-methyl) ester. M.p. 45 - 47°C.

b) One added 0.24 g (0.83 mmol) of this compound to a solution of 23 mg sodium hydride and 0.46 g (0.75 mmol) of the compound of Example 92h) in 3 ml dimethylformamide, stirred for 8 h at 110°C, poured on to water, extracted with ethyl acetate, removed the solvent in a vacuum and obtained 300 mg (55%) N-(2,2-dimethyl-1,3-dioxolan-4-yl-methyl)-N-{3-[2-(benzyltetrachloropyridin-4-ylamino)-ethoxy]-5-methylphenyl}-benzenesulphonamide as oil. MS (m/e) = 725.

c) One obtained N-(2,3-dihydroxypropyl)-N-{3-[2-(benzyltetrachloropyridin-4-ylamino)-ethoxy]-5-methylphenyl}-benzenesulphonamide (38%, m.p. 133 - 136°C) from this compound analogously to Example 92j).

d) One obtained the title compound (66%, amorphous, MS (m/e) = 457) from this compound analogously to Example 96k).

Example 103

4-(Benzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-butyric acid ethyl ester

One obtained the following compounds analogously to Examples 92i) to 92k) in that one used 4-bromo-butyric acid ethyl ester in Example 92i) instead of bromoacetic acid ethyl ester: 4-(benzenesulphonyl-{3-methyl-5-[2-(benzyltetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-aminobutyric acid ethyl ester (78%, m.p. 106 - 108°C; 4-(benzenesulphonyl)-{3-methyl-5-[2-(tetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-amino)-butyric acid ethyl ester (oil, MS (m/e) = 633); title compound (75%, amorphous, MS (m/e) = 497).

Example 104

5-(Benzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-pentanoic acid ethyl ester

One obtained the following compounds analogously to Examples 92i) to 92k) in that one used 5-bromo-pentanoic acid ethyl ester in Example 92i) instead of bromoacetic acid ethyl ester: 5-(benzenesulphonyl-{3-methyl-5-[2-(benzyltetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-amino)-pentanoic acid ethyl ester (72%, m.p. 90 - 91°C); 5-(benzenesulphonyl-{3-methyl-5-[2-(tetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-amino)-pentanoic acid ethyl ester (86%, oil, MS (m/e) = 647); title compound (78%, amorphous, MS (m/e) = 511).

Example 105

6-(Benzenesulphonyl-{3-methyl-5-[2-(pyridin-ylamino)-ethoxy]-phenyl}-amino)-hexanoic acid ethyl ester

One obtained the following compounds analogously to Examples 92i) to 92k) in that one used 6-bromo-hexanoic acid ethyl ester in Example 92i) instead of bromoacetic acid ethyl ester: 6-(benzenesulphonyl-{3-methyl-5-[2-(benzyltetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-amino)-hexanoic acid ethyl ester (75%, oil, MS (m/e) = 751); 6-(benzenesulphonyl-{3-methyl-5-[2-(tetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-amino)-hexanoic acid ethyl ester (49%, oil, MS (m/e) = 661); title compound (56%, amorphous, MS (m/e) = 525).

Example 106

4-(Benzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-butyric acid

was obtained analogously to Example 93) from the compound of Example 103). 65% yield, amorphous, MS (m/e) = 469.

Example 107

5-(Benzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-pentanoic acid

was obtained analogously to Example 93) from the compound of Example 104). 53% yield, m.p. 117 - 120°C.

Example 108

6-(Benzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-hexanoic acid

was obtained analogously to Example 93) from the compound of Example 105). 53% yield, amorphous, MS (m/e) = 498.

Example 109

2-Methoxy-benzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy½-phenyl}-amino)-acetic acid ethyl ester

One obtained the following compounds analogously to Examples 92h) to 92k) in that one used 2-methoxy-benzenesulphonyl chloride in step 92h) instead of benzenesulphonyl chloride: 2-methoxy-N-{3-[2-benzyl-tetrachloropyridin-4-ylamino)-ethoxy]-5-methylphenyl}-benzenesulphonamide (65%, m.p. 175°C); (2-methoxy-benzenesulphonyl-{3-methyl-5-[2-(benzyltetrachloro-pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetic acid ethyl ester (91%, m.p. 128 - 130°C); (2-methoxybenzene-sulphonyl-{3-methyl-5-[2-(tetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetic acid ethyl ester (89%, m.p. 126°C); title compound (81%, m.p. 58 -63°C).

Example 110

2-Methoxybenzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetic acid

was obtained from the compound of Example 109) analogously to Example 93). 82%, m.p. 218 - 222°C.

Example 111

(2-Methoxybenzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained analogously to Example 94) from the compound of Example 109. (63%, m.p. 205°C).

Example 112

N-(2-Hydroxyethyl)-(2-methoxybenzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in 33% yield analogously to Example 95 from the compound of Example 109. M.p. 175°C.

Example 113

N-(3-Hydroxypropyl)-(2-methoxybenzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in 95% yield analogously to Example 96 from the compound of Example 109. M.p. 165 - 167°C.

Example 114

N-Methyl-(2-methoxybenzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in 96% yield analogously to Example 97 from the compound of Example 109. Amorphous. MS (m/e) = 484.

Example 115

N,N-Dimethyl-(2-methoxybenzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in 73% yield analogously to Example 98 from the compound of Example 109. Amorphous. MS (m/e) = 498.

Example 116

N-(2-Aminoethyl)-(2-methoxybenzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in 93% yield analogously to Example 99 from the compound of Example 109. Amorphous. MS (m/e) = 513.

Example 117

N-(2,3-Dihydroxypropyl)-(2-methoxybenzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetamide

was obtained in 75% yield analogously to Example 101 from the compound of Example 109. Amorphous. MS (m/e) = 544.

Example 118

(2-Methoxybenzenesulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetonitrile

One added 250 µl trichloroacetyl chloride in 0.5 ml dichloromethane at 0°C to 94 mg (0.2 mmol) of the compound of Example 111 in 0.5 ml dichloromethane and 60 µl triethylamine. After 5 min, one neutralised with triethylamine, removed the solvent in a vacuum and filtered the residue over silica gel (ethyl acetate/methanol, ammonia = 4:1). One obtained 60 mg of the title compound as amorphous mass. MS (m/e) = 452.

Example 119

N-(2-Aminoethyl)-N-{3-[2-pyridin-4-ylamino)-ethoxy]-5-methylphenyl}-2-methoxybenzenesulphonamide

One obtained (2-methoxybenzenesulphonyl-{3-methyl-5-[2-(benzyltetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetonitrile (92%, m.p. 154°C) by reacting 2-methoxy-N-{3-[2-(benzyltetrachloropyridin-4-ylamino)-ethoxy]-5-methylphenyl}-benzenesulphonamide (Example 109 with chloroacetonitrile analogously to Example 92i), from which one obtained (2-methoxybenzenesulphonyl-{3-methyl-5-[2-(tetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetonitrile analogously to Example 92j) (85%, amorphous, MS (m/e) = 588) which was reacted analogously to Example 92k) to give the title compound (10%, amorphous, MS (m/e) = 456).

Example 120

2-{3-[2-(Benzylpyridin-4-ylamino)-ethoxy]-5-methyl-phenylsulphamoyl}-benzoic acid methyl ester

a) One reacted 4-toluenesulphonic acid 2-(benzyl-tetrachloropyridin-4-ylamino)-ethyl ester (Example 92e) with 3-nitrophenol analogously to Example 92f) and obtained N-benzyl-N-(tetrachloropuridin-4-yl)-N-[2-(3-nitrophenoxy)-ethyl]-amine. (61%, 120 - 122°C).

b) One reduced this compound analogously to Example 79a) and obtained N-benzyl-N-(tetrachloropyridin-4-yl)-N-[2-(3-aminophenoxy)-ethyl]-amine (41%, 105 - 107°C).

c) One reacted this compound analogously to Example 92h) to give N-{3-[2-(benzyltetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-benzenesulphonamide. (78%, m.p. 120 - 122°C).

d) One hydrogenated this compound analogously to Example 92k) and obtained the title compound (63%, amorphous, MS (m/e) = 517).

Example 121

[2-(Methyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy-phenyl}-sulphamoyl)-phenoxy]-acetic acid ethyl ester

a) One reacted N-benzyl-N-(tetrachloropyridin-4-yl)-N-[2-(3-amino-5-methylphenoxy)-ethyl]-amine (Example 92g) analogously to Example 92h) with 2-benzyloxy-benzenesulphonyl chloride and obtained N-{3-[2-(benzyltetrachloropyridin-4-ylamino)-ethoxy]-5-methylphenyl}-2-benzyloxybenzenesulphonamide. (55%, m.p. 176°C).

b) One methylated this compound analogously to Example 12) and obtained N-methyl-N-{3-[2-(benzyltetrachloro-pyridin-4-ylamino)-ethoxy]-5-methylphenyl}-2-benzyloxybenzenesulphonamide (78%, amorphous, MS (m/e) = 729).

c) One obtained N-methyl-N-{3-[2-(tetrachloropyridin-ylamino)-ethoxy]-5-methylphenyl}-2-hydroxybenzene-sulphonamide from this compound analogously to Example 92j) (87%, amorphous, MS (m/e) = 549).

d) One reacted this compound analogously to Example 18) to give [2-(methyl-{3-methyl-5-[2-(tetrachloro-pyridin-4-ylamino)-ethoxyphenyl}-sulphamoyl)-phenoxy]-acetic acid ethyl ester (quant., oil, MS (m/e) = 635).

e) One hydrogenated this compound analogously to Example 92k) and obtained the title compound (50%, amorphous, MS (m/e) = 499).

Example 122

N-{3-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-hydroxybenzenesulphonamide

a) One reacted N-{3-[2-(benzyltetrachloropyridin-4-ylamino)-ethoxy]-5-methylphenyl}-2-benzyloxybenzene-sulphonamide (Example 121a) analogously to Example 92j) to give N-{3-[2-(tetrachloropyridin-4-ylamino)-ethoxy]-5-methylphenyl}-2-hydroxybenzenesulphonamide (70%, amorphous, MS (m/e) = 535).

b) One obtained the title compound therefrom analogously to Example 92k). (81%, amorphous, MS (m/e) = 399).

Example 123

N-Methyl-N-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-hydroxybenzenesulphonamide

One reacted N-methyl-N-{3-[2-(benzyltetrachloro-pyridin-4-ylamino)-ethoxy]-5-methylphenyl}-2-benzyloxy-benzenesulphonamide (Example 121b) analogously to Example 122) and obtained N-methyl-N-{3-[2-(tetra-chloropyridin-4-ylamino)-ethoxy]-5-methylphenyl}-2-hydroxybenzenesulphonamide (65%, amorphous, MS (m/e) = 549) and the title compound (27%, amorphous, MS (m/e) = 413).

Example 124

[2-(Methyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-sulphamoyl)-phenoxy]-acetic acid

a) One saponified [2-(methyl-{3-methyl-5-[2-(tetrachloropyridin-4-ylamino)-ethoxy]-phenyl}-sulphamoyl)-phenoxy]-acetic acid ethyl ester (Example 121d) analogously to Example 93) and obtained [2-(methyl-{3-methyl-5-[2-(tetrachloropyridin-4-ylamino)-ethoxy-phenyl}-sulphamoyl)-phenoxy]-acetic acid (94%, amorphous, MS (m/e) = 607).

b) One obtained the title compound therefrom analogously to Example 92k) (75%, amorphous, MS (m/e) = 471).

Example 125

N-Ethoxycarbonyl-N-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-methoxybenzenesulphonamide

a) One reacted 2-Methoxy-N-{3-[2-benzyltetrachloropyridin-4-ylamino)-ethoxy]-5-methylphenyl}-benzenesulphonamide (Example 109) analogously to Example 92i) with chloroformic acid ethyl ester and obtained N-ethoxycarbonyl-N-{3-[2-(benzyltetrachloropyridin-4-ylamino)-ethoxy]-5-methylphenyl}-2-methoxybenzenesulphonamide (quant., amorphous, MS (m/e) = 711).

b) One obtained therefrom N-ethoxycarbonyl-N-{3-[2-(tetrachloropyridin-4-ylamino)-ethoxy]-5-methyl-phenyl}-2-methoxybenzenesulphonamide analogously to Example 92j) (80%, m.p. 156°C).

c) One obtained the title compound therefrom analogously to Example 92k) (66%, amorphous, MS (m/e) = 485).

Example 126

N-(2-Hydroxyethyl)-N-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-2-methoxybenzenesulphonamide

One added 24 mg (0.6 mmol) lithium aluminium hydride to 150 mg (0.3 mmol) (2-methoxybenzene-

sulphonyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-amino)-acetic acid ethyl ester (Example 109) in 5 ml dry tetrahydrofuran and heated for 2 h under reflux. One decomposed with 1 drop of water and 3 drops of 2 N hydrochloric acid, filtered and removed the solvent in a vacuum. One filtered the residue over 50 g silica gel (methylene chloride/methanol = 4:1) and obtained 50 mg (36%) of the title compound as amorphous solid. MS (m/e) = 457.

Example 127

N-{3-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-pyridin-3-sulphonamide

was obtained analogously to Example 57) in that one used 3-pyridinesulphonyl chloride in step 57d). Amorphous. MS (m/e) = 385.

Example 128

Description of pharmacological experiments

Thrombin time

The thrombin time is a conventional test in clinical coagulation diagnostics. This parameter measures the action of thrombin on fibrinogen and the formation of clots. Inhibitors of thrombin bring about a prolongation of the thrombin time.

For the obtaining of plasma, 9 parts of fresh blood from healthy donors was mixed with one part of sodium citrate solution (0.11 mol/l) and centrifuged for 10 min. at room temperature at ca. 3000 r.p.m. The plasma was pipetted off and can be stored at room temperature for ca. 8 hours.

200 µl citrate plasma were incubated for 2 min. at 37°C in a ball coagulometer (KC10 from the firm Amelung). One added 10 µl dimethylsulphoxide (DMSO) or a solution of the active substance in DMSO to 190 µl preheated thrombin reagent (Boehringer Mannheim GmBH; contains ca. 3 U/ml horse thrombin and 0.0125 M

Ca^{++}). With addition of 200 µl of this solution to the plasma, a stopwatch was started and the time up to the commencement of coagulation was determined. The thrombin time was ca. 24 sec. in control measurements and was distinctly increased by the active substances. If the thrombin time in the presence of an exemplary compound was longer than 5 min., the experiment was discontinued.

The measured thrombin times in seconds are given in the following Table as difference to control. The concentrations of the active substances in the final volume amounted to 250 µM (TT250), 25 µM (TT25) and 2.5 µM (TT2.5).

Thrombin inhibition

The kinetic measurements were carried out in 0.1 M phosphate buffer which contained 0.2 M common salt and 0.5% polyethylene glycol 6000 at a pH = 7.5 and 25°C with the substrate H-(D)-Phe-Pro-Arg-pNA (S-2238 Kabi) and human ∝-thrombin (Sigma, specific activity = 2150 NIH units/mg) in polystyrene semi-microcuvettes in a total volume of 1 ml.

In a preliminary test, with each active substance was determined whether it inhibits thrombin rapidly or slowly. For this purpose, the reaction was firstly started by addition of 0.03 NIH units thrombin to a 100 µM solution of the substrate and of the active substance. In a second experiment, substrate was added to a solution of thrombin and of the active substance incubated for 5 min. The increase of the concentration of p-nitroaniline with time was monitored spectroscopically (UV-VIS spectrophotometer Lambda-2 from the firm Perkin-Elmer) at 405 nm for 12 min. Since the measured curves obtained in both experiments were linear and parallel, in the case of the active substances of the following Table, it is a question

of rapid thrombin inhibitors. The inhibition constants K_i were then determined as follows. The substrate was used at concentrations of 100 µM, 50 µM, 30 µM, 20 µM and at each substrate concentration a measurement was carried out without inhibitor and three measurements in the presence of different concentrations of the inhibitors listed in the following Table. The reactions were started by addition of thrombin. The increase of the extinction at 405 nm due to the resulting p-nitroaniline was monitored over a time period of 12 min. Measurement points (time versus absorbance) were transferred to a PC at intervals of 20 sec. The rates V_o (extinction change per sec.; measurements without inhibitor) and V_i (measurements with inhibitor) were determined by linear regression. Only that part of the measurement was used in which the substrate concentration had decreased by less than 15%. One determined K_m and V_{max} from a measurement series (constant inhibitor concentration, variable substrate concentrations) by a non-linear fit to the equation

$$V = \frac{V_{max}*[S]}{[S] + K_m}$$

Finally, from the entire series of measurements, one calculated K_i by non-linear fitting to the equation

$$V = \frac{V_{max}*[S]}{K_m*(1 + [S]/K_i) + [S]}$$

The Michaelis constant K_m amounted to 3.8 ± 2 µM in all measurements.

The inhibition constants K_i of the active substances are given in the following Table in units of µM.

Inhibition of trypsin and plasmin

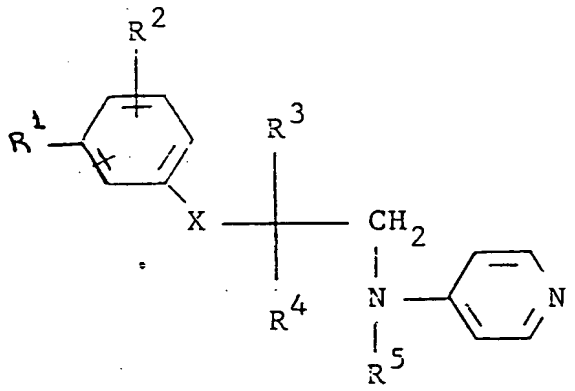
10 mg bovine pancreatic trypsin (Sigma) were dissolved in 100 ml 1 mM hydrochloric acid and stored in a refrigerator. 20 µl thereof were mixed with 980 µl 1 mM hydrochloric acid. 25 µl thereof were used for each measurement. The measurement was carried out as described for thrombin. K_m = 45 µM. The substances listed in the following Table do not inhibit trypsin (K_i > 400 µM).

The measurements with human plasmin (Sigma, 10 units) were carried out as described for thrombin with the substrate S-2251 (H-(D)-Val-Leu-Lys-pNA, Kabi). 0.01 units of plasmin were used per measurement. K_m = 250 µM. The substances listed in the following Table do not inhibit plasmin (K_i > 400 µM).

Example No.	K_i thrombin	TT250	TT25	TT2.5
2	0.300	150	40	6
8	1.000	288	58	13
10	3.000	157	43	7
15	0.130	270	144	15
48	0.600	300	238	46
59	6.000	53	8	0
60	0.600	137	62	13
72	0.024	300	300	159
79	5.000	30	8	0
80	0.150	300	213	44
83	0.100	300	192	48
86	0.040	300	167	11
89	1.000	132	38	6
90	0.024	300	300	125
100	0.083	300	300	186
108	0.055	300	300	62
124	0.250	300	300	104
125	0.150	300	273	73

Patent Claims

1. 4-Aminopyridines of the general formula I



(I)

in which

R^1 denotes the group R^6-SO-NR^7-, R^6-SO_2-NR^7-, R^6-NR^7-SO-, R^6-NR^7-SO_2-, R^6-SO-O-, R^6-SO_2-O-, R^6-O-SO- or R^6-O-SO_2-,

R^2 denotes a hydrogen or halogen atom, a cyano, C_1-C_6-alkyl, C_1-C_6-alkoxy or halo-C_1-C_6-alkyl group,

X denotes an oxygen atom, a sulphur atom or the NH group,

R^3 and R^4 are the same or different and denote hydrogen atoms or alkyl groups,

R^5 denotes a hydrogen atom, a C_1-C_6-alkyl group or the aralkyl group,

R^6 denotes a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, aryl, aralkyl or a mono-, bi- or tricyclic aromatic system with heteroatoms, such as nitrogen, oxygen and sulphur, which can be linked with a C_1-C_6-alkyl group, which, like the aryl radical, can be substituted one or several times by nitro, halogen, nitrile, hydroxy, amino, carboxy, C_1-C_6-alkoxycarbonyl, C_2-C_6-alkenyloxy-carbonyl, C_2-C_6-alkenyloxycarbonyl, C_2-C_6-alkynyloxy-carbonyl, aralkoxycarbonyl, C_1-C_6-alkyl, C_3-C_7-cyclo-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, cyano-C_2-C_6-alkyl,

C_1-C_6-alkoxy, C_2-C_6-alkenyloxy, C_2-C_6-alkynyloxy, aralkyloxy, cyano-C_1-C_6-alkyloxy, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, aralkylamino, diaralkylamino, C_1-C_6-alkylsulfonylamino, C_1-C_6-alkylcarbonylamino, formylamino, aminocarbonyl, C_1-C_6-alkylaminocarbonyl, di-C_1-C_6-alkylaminocarbonyl or by one or more of the groups -Y-CO_2R^8, -S-Y-CO_2R^8, -O-Y-CO_2R^8, -NH-Y-CO_2R^8, -S-Y-$CONR^8R^9$, -O-Y-$CONR^8R^9$, whereby the alkyl, alkenyl or alkynyl fragments can be substituted one or more times by halogen, hydroxy, C_1-C_6-alkoxy, C_1-C_6-alkylcarbonyloxy, amino or carboxy groups,

R^7 denotes a hydrogen atom, a C_1-C_6alkyl, C_3-C_7-cycloalkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl radical, whereby these radicals can be substituted one or more times by halogen, hydroxy, C_1-C_6-alkoxy, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, carboxy, C_1-C_6-alkylcarbonyl or C_1-C_6-alkoxycarbonyl, or denote the C_1-C_6-alkoxycarbonyl, cyano-C_1-C_6-alkyl, aryl, aralkyl or a mono-, bi- or tricyclic aromatic system with heteroatoms, such as nitrogen, oxygen and sulphur, which can be linked with a C_1-C_6-alkyl group which, like the aryl radical, can be substituted one or more times by halogen, nitrile, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyloxy, C_2-C_6-alkynyloxy, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, halo-C_1-C_6-alkoxy, hydroxy, carboxy, hydroxy-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, C_1-C_6-alkylsulfonylamino, C_1-C_6-alkylcarbonylamino, formylamino, aminocarbonyl or phenyl, or denotes a group -Y-CO_2R^8 or -Y-$CONR^8R^9$ group,

Y denotes a linear or branched C_1-C_6-alkylene chain,

R^8 and R^9 are the same or different and denote hydrogen atoms, aralkyl, C_3-C_7-cycloalkyl or C_1-C_6-alkyl groups, which can be substituted one or more times by halogen, hydroxy, C_1-C_6-alkoxy, C_1-C_6-alkylcarbonyloxy, amine or carboxy, or R^8 and R^9, together with the N atom to which they are bound, form a saturated ring which can contain an additional oxygen, sulphur or nitrogen atom,

as well as hydrates, solvates and physiologically compatible salts thereof, and their optically-active forms, racemates and diastereomeric mixtures.

2. 4-Aminopyridines of formula I according to claim 1, characterised in that R^1 denotes R^6-SO-NR^7-, R^6-NR^7-SO_2-, R^6-SO_2-O- or R^6-O-SO_2.

3. 4-Aminopyridines of formula I according to claim 1 or 2, characterised in that R^2 denotes a hydrogen, chlorine or bromine atom, or a C_1-C_6-alkyl group, a C_1-C_6-alkoxy group or the trifluoromethyl group.

4. 4-Aminopyridines of formula I according to one of the claims 1 to 3, characterised in that X denotes an oxygen atom or the NH group.

5. 4-Aminopyridines of formula I according to one of the claims 1 to 4, characterised in that R^3 and R^4 are the same or different and represent hydrogen atoms or C_1-C_6-alkyl groups.

6. 4-Aminopyridines of formula I according to one of the claims 1 to 5, characterised in that R^5 represents a hydrogen atom, a C_1-C_6-alkyl group or the benzyl group.

7. 4-Aminopyridines of formula I according to one of the claims 1 to 6, characterised in that R^6 denotes a C_1-C_6-alkyl group, a C_3-C_7-cycloalkyl group, an unsubstituted phenyl or benzyl group or a phenyl or

benzyl group substituted one or more times by fluorine, chlorine, C_1-C_6-alkyl, C_1-C_6-alkoxy, nitro, amino, hydroxy, carboxy, benzyloxycarbonyl, C_1-C_6-alkoxy-carbonyl, trifluoromethyl or the group $-O-Y-CO_2R^8$; a naphthyl, tetrahydronaphthyl, biphenyl or indanyl group, a thienyl, pyrazolyl or pyridyl, benzthienyl or benzothiadiazinyl group.

8. 4-Aminopyridines of formula I according to one of the claims 1 to 7, characterised in that R^7 denotes a hydrogen atom, a C_1-C_6-alkyl, C_2-C_6-alkenyl group or an aralkyl group, a C_1-C_6-alkoxycarbonyl group, a cyanoalkyl group, a hydroxyalkyl group or an aminoalkyl group, a group $-Y-COR^8$ or a group $-Y-CONR^8R^9$.

9. 4-Aminopyridines of formula I according to one of the claims 1 to 8, characterised in that Y denotes a methylene, propylene, butylene or pentylene group.

10. 4-Aminopyridines of formula I according to one of the claims 1 to 9, characterised in that R^8 denotes a hydrogen atom or a C_1-C_6-alkyl group, a hydroxy-C_1-C_5-alkyl group or an amino-C_1-C_6-alkyl group.

11. 4-Aminopyridines of formula I according to one of the claims 1 to 10, characterised in that R^9 denotes a hydrogen atom or a $-C_1$-C_6-alkyl group.

12. Medicaments containing at least one compound of formula I according to one of the claims 1 to 11, besides pharmaceutical carrier and auxiliary substances.

13. Use of compounds of formula I according to one of the claims 1 to 11 for the production of medicaments for the treatment of thromboembolic diseases.